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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**: $(PCy_3)_2Cl_2Ru{=}CHPh$).[2b-d] Mechanistic investigations[3] indicate that dissociation[3e] of the tricyclohexylphophine (PCy_3) to the four-coordinate 14-electron species ($LCl_2Ru{=}CHPh$)[3b] is crucial. However, surprisingly, **1-Me** only dissociates PCy_3 less efficiently than **2**.[3c,d] Therefore, in effort to enhance the catalytic activity of **1-Me**, phosphine-free catalysts were prepared by replacing PCy_3 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) moiety[5] 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 cite are requisite. We have already developed very efficient ligands of this nature, i.e., bowl-shaped phosphines[6] 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 decompositions[9] 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 PCy_3 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-isopropoxystyrene[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

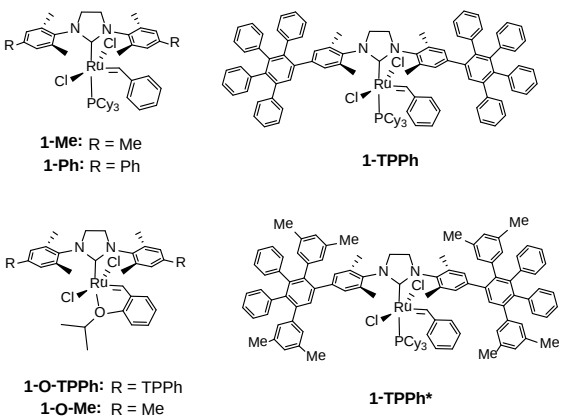


Fig. 1 Structures of catalysts.

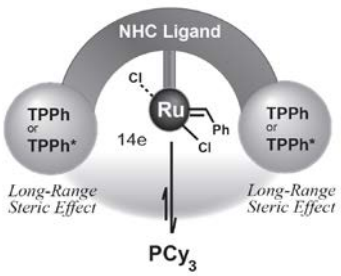


Fig. 2 Ru metathesis catalyst activated by the long-range steric effect

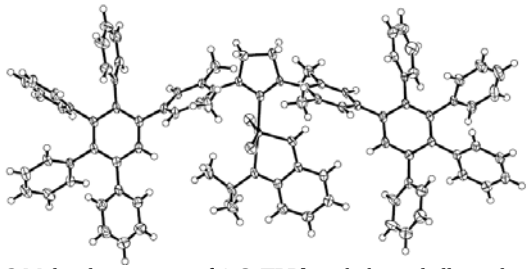
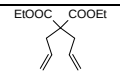
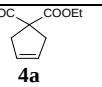
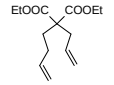
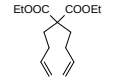
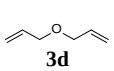
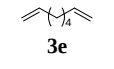


Fig. 3 Molecular structure of **1-O-TPPh** with thermal ellipsoids at 50% probability levels.

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	**3a**	**4a**	**1-Ph**		57
4			**1-O-TPPh**		48
5			**1-TPPh**	8	99 (99)[c]
6			**1-Me**		54
7	**3b**	**4b**	**1-Ph**		51
8			**1-TPPh**	6	99 (72)[c]
9			**1-Me**		38
10	**3c**	**4c**	**1-Ph**		29
11[d]			**1-TPPh**	5	74
12[d]			**1-Me**		10
13[d]	**3d**	**4d**	**1-Ph**		5
14[d]			**1-TPPh**	5	88
15[d]			**1-Me**		51
16[d]	**3e**	**4e**	**1-Ph**		46

[a] Diolefin (0.25 mmol), catalyst (2.5 μmol, 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 CH_2Cl_2 (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 CH_2Cl_2 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 substantially occur.

Table 2 Effect of added PCy_3 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

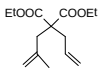
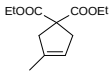
[a] **3a** (0.25 mmol), catalyst (2.5 μmol, 1.0 mol%), added PCy_3 (0.25 μmol: 0.10 mol% or 0.50 μmol, 0.20 mol%), in toluene (5.0 mL), at 0 °C for 17 h. [b] Yield of the product based on the GC internal standard technique.

When 0.10 mol% of PCy_3 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 PCy_3 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 PCy_3 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 PCy_3 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 PCy_3, even **1-TPPh** lowered its catalytic activity.

Hence, we tried to remove PCy_3 from the catalyst systems by adding CuCl as a phosphine scavenger[12] (generating ill-characterized CuCl-PCy_3 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 PCy_3 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% yield[13] 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/

‡ Crystallographic data of **1-O-TPPh**: $C_{92}H_{80}Cl_8N_2ORu$, M = 1614.35, triclinic, space group $P\bar{1}$ (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) Å^3, Z = 2, 16946 independent reflections (R_{int} = 0.065), $R1(I > 2\sigma(I))$ = 0.0857, $wR2$ (all data) = 0.1643. GOF = 1.321. CCDC 82559.

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