Bidentate *N*,*O*-prolinate ruthenium benzylidene catalyst highly active in RCM of disubstituted dienes†

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The synthesis of a bidentate *N*,*O*-prolinate ruthenium benzylidene from commercially available starting materials and its activity in ring-closing metathesis of functionalized disubstituted dienes at 30 °C is disclosed.

Ring-closing metathesis (RCM) has been established as a powerful and efficient synthetic tool for carbon–carbon double bond formation leading to carbo- and heterocycles.[1] Whereas there are several catalysts that have been reported for RCM, the ruthenium-based catalysts have received considerable attention because they provide catalytic systems more tolerant to a large number of organic functional groups, moisture, and oxygen (Fig. 1).[2] In an ongoing project, we are interested in using chiral chelating ligands for asymmetric induction in metathesis reactions. One problem to overcome with a chelated catalyst is to maintain high activity in metathesis reactions. Previously, we reported the synthesis and reactivity of different Ru-based catalysts with bidentate Schiff-base alkoxide ligands (Fig. 1, complex **4**).[3] These catalysts showed low activity at room temperature; however, at elevated temperature their reactivity increased dramatically.[4] Unfortunately, the synthesis of alkoxide-containing catalysts usually involves and generates undesirable toxic thallium salts. Other chelated catalysts have also been reported.[5] We wanted to investigate whether the reactivity of similar *N*,*O*-bidentates could be increased by exchanging the alkoxide for a more electron-withdrawing carboxylate.[6] Furthermore, the use of cheap, readily available reagents was beneficial. Herein, we report the synthesis and reactivity of bidentate *N*,*O*-prolinate Ru benzylidene (**5**).

Synthesis of bidentate *N*,*O*-prolinate Ru benzylidene **5** involves commercially available and cheap starting materials and is performed on the bench top using standard Schlenk techniques. Reaction of 1st generation Grubbs catalyst (**1**) with proline and Cu_2O in CH_2Cl_2 gives complex **5** in 40% yield after column chromatography (Scheme 1). The structure was assigned by ^1H, ^{13}C, ^{31}P NMR, IR, and mass spectroscopy (see ESI†). Complex **5** shows characteristic signals in the ^1H NMR spectrum at δ 19.62 ppm corresponding to the benzylidene (d, J_{P-H} = 11.2 Hz, 1H), in the ^{31}P NMR spectrum at δ 43.9 ppm (s) corresponding to the coordinated PCy_3, and in the ^{13}C NMR spectrum at δ 305 ppm (d, J_{P-C} = 14.5 Hz) corresponding to the carbene carbon. Complex **5** shows an IR spectrum with an NH band at 3200 cm^{-1} and a C=O band at 1604 cm^{-1}.

Complex **5** was found to be an active catalyst at 30 °C for ring-closing metathesis of diethyl diallylmalonate, with conversion above 90% within 1 h. The high activity of catalyst **5** has its origin in the electron-withdrawing carboxylate. If the carboxylate is exchanged for an alkoxide in an analogous complex very low activity is observed (less than 10% after 5 h).[7] To quantify the activity of catalyst **5**, the reaction was run at 30 °C and followed by ^1H NMR spectroscopy and compared to complexes **1** and **2** (Fig. 2).[8] Both catalysts **1** and **2** initiate faster than **5** and catalyst **2** reaches above 90% conversion within 20 min (Fig. 2). However, while complex **1** only reaches 60% conversion in one hour, **5** proceeds to >90% conversion. Catalyst **5** is stable and follows 1st order kinetics over 4 half-lives.†

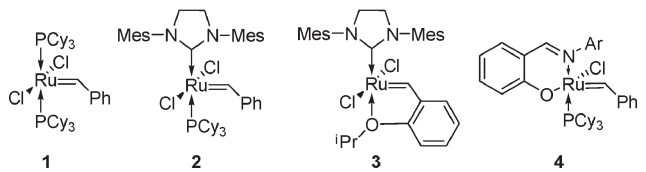
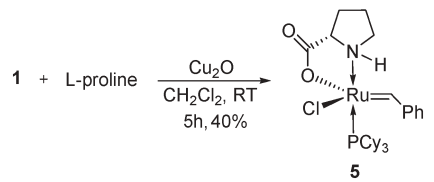


Fig. 1 Ru-based metathesis catalysts.



Scheme 1 Synthesis of catalyst **5**.

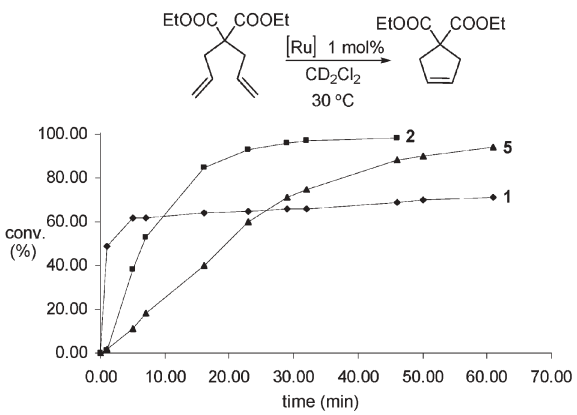


Fig. 2 Ring-closing of diethyl diallylmalonate by **1**, **2**, and **5**.

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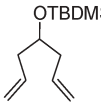
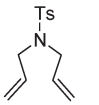
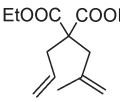
† Electronic supplementary information (ESI) available: Experimental procedures and spectral data for compound **5**. See DOI: 10.1039/b704821a

Table 1 RCM of different substrates by **5**[a]

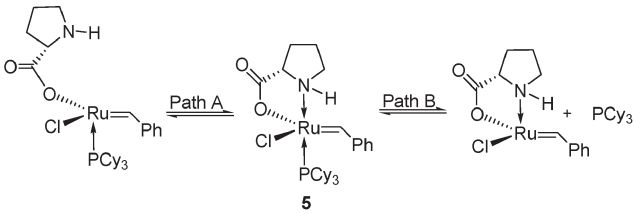
Entry	Substrate	Time	Yield[b]
1		40 min	>95%
2		60 min	>95%
3		90 min	>95%
4		180 min	>95%
5[c]		16 h	80%

[a] Reactions were performed on a 0.08 mmol scale in CD_2Cl_2 (0.75 ml) at 30 °C using 1 mol% of **4**. [b] Determined by ^1H NMR spectroscopy. [c] 2 mol% of **4** was used.

Our group previously reported that the efficiencies of the metathesis activities for catalysts **1** and **2** could be increased by addition of CuCl.[9] The scavenger is believed to activate the catalyst by removing the phosphine ligand from solution and thereby freeing up a coordination site on the metal center. In the presence of CuCl, catalyst **5** was indeed more active and reached >90% conversion within 20 min! However, the catalyst is not stable under these reaction conditions and does not follow first order kinetics.

To investigate the substrate scope and the functional group tolerance for catalyst **5**, different substrates were tested. The reactions were run using 1 mol% catalyst at 30 °C in CD_2Cl_2 and were followed by ^1H NMR spectroscopy to above 95% conversion. 1,7-Octadiene was smoothly ring-closed to cyclohexene within 40 min (Table 1, entry 1). *tert*-Butyl(hetpa-1,6-dien-4-yloxy)dimethylsilane was also converted to the corresponding cyclopentene within 60 min (Table 1, entry 2). Diallyl ether was ring-closed to 3,4-dihydrofuran in 90 min with above 95% selectivity (Table 1, entry 3). No isomerization to 2,3-dihydrofuran was observed under the course of the reaction.[10] Also *N*,*N*-diallyl-*p*-toluenesulfonamide was smoothly converted into product within 3 h (Table 1, entry 4). Diethyl allylmethylallylmalonate was ring-closed to form the trisubstituted product in 80% after 16 h (Table 1, entry 5).

To further investigate the scope of catalyst **5** ring-opening metathesis polymerization (ROMP) of 1,5-cyclooctadiene was run at 30 °C. In 12 h, 80% conversion was reached. Unfortunately, desymmetrization of trienes gave poor enantioselectivity.[11–14] This could be explained by a number of different reasons. Initially, we thought that the small size of the COO in the L-prolinate was responsible for the lack of chiral induction. Therefore, the COO was exchanged for CONTs, with more steric bulk in the vicinity of Ru. Unfortunately, this had no effect on the ee. One of the referees pointed out that the low ee could be explained by a fast racemization of the prolinate ligand. However, no increase in ee was observed when the reaction was run in the presence of benzoquinone.[10]



Scheme 2 Possible dissociation pathways for catalyst **5**.

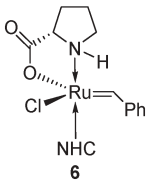


Fig. 3 Phosphine free analog.

From a mechanistic point of view, either the *N*-heterocyclic moiety of proline (Scheme 2, Path A) or the tricyclohexylphosphine (Scheme 2, Path B) can dissociate from Ru to form the active 14-electron intermediate as the first step in the catalytic cycle. To distinguish between the two different pathways is difficult. When the RCM of diethyl diallylmalonate is run in the presence of PCy_3 (2 equivalents with respect to **5**) the catalysis is nearly shut off (less than 5% conversion in 1 h compared to above 90% conversion, see Fig. 2). However, the free PCy_3 could coordinate to either free coordination-site of ruthenium (Scheme 2).

We recently found a CuCl rate enhancement for a phosphine-free analog **6** of parent catalyst **5**, where an *N*-heterocyclic carbene is positioned at the equivalent position of PCy_3 in **5** (Fig. 3).[15] We believe that one explanation for the low enantioselectivity found in the desymmetrization experiment could originate from a favored amine to phosphine dissociation as the first step in the catalytic cycle (Scheme 2), where the remaining monodentate carboxylate gives no chiral induction.

The synthesis of bidentate *N*,*O*-prolinate Ru benzylidene (**5**) using non-toxic commercially available and cheap starting materials has been described. Complex **5** was found to be an efficient catalyst for RCM of disubstituted dienes with high activity. The electron-withdrawing carboxylate of proline is crucial for the activity of catalyst **5** at 30 °C, with rates comparable to **1**. The mechanism for the initiation of catalyst **5** is not yet fully understood and is currently under investigation.

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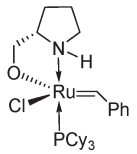

alkoxide analog of **5**

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