Testing New Ruthenium Complexes bearing Chiral 1,2,4-Triazol-5-ylidene Ligands as Catalysts for Asymmetric Olefin Metathesis

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Abstract: New ruthenium complexes bearing chiral 1,2,4-triazol-5-ylidene ligands were obtained and tested in model asymmetric metathesis reactions. Low enantioselectivity in asymmetric ring-closing metathesis (ARCM) and moderate enantioselectivity in asymmetric ring-opening/ring-closing metathesis (AROCM) was observed.

Key words: ruthenium, carbene complexes, NHC, olefin metathesis, asymmetric catalysis

In the past ten years, enantioselective olefin metathesis has emerged as a powerful method for the synthesis of carbon–carbon double bonds with simultaneous creation of chirality elements under mild reaction conditions. These advances have been possible due to intensive efforts in the area of transition metal catalyst design. As it was shown in a number of synthetic studies, chiral Mo-, W-, and Ru-based catalysts used in asymmetric olefin metathesis are complementary regarding scope and limitations.[1]

In the ruthenium kingdom, since the first report[2] on complexes **1** and **2** (Figure 1), a number of catalysts bearing NHC ligands derived from chiral 1,2-diamines have been developed by Grubbs (**2**),[2] Collins (**3**)[3] and others. Hoveyda introduced a conceptually unique class of Ru catalysts (**4**) bearing C_1-symmetric bidentate NHC ligands.[4] Recently, Blechert reported on the synthesis of complexes **5** and **6a**,**b** with high activity and selectivity.[5] Collins and Blechert showed that C_1-symmetric complexes give higher enantioselectivity in model reactions.[3,5]

Chiral 1,2,4-triazolium salts (e.g. **7a**,[6] Scheme 1) were used with great success in a number of organocatalytic transformations[7] and were also recently applied as ligand precursors for transition metal catalysis.[8,9] This encouraged us to investigate the possibility of using them for ruthenium-catalyzed asymmetric olefin metathesis.

Herein, we report on the synthesis of chiral ruthenium metathesis (pre)catalysts bearing C_1-symmetric 1,2,4-triazol-5-ylidenes and their evaluation in model asymmetric olefin metathesis reactions.

We started with precursor **7a**[6] (Scheme 1) because of its rigid structure and commercial availability. Treatment of

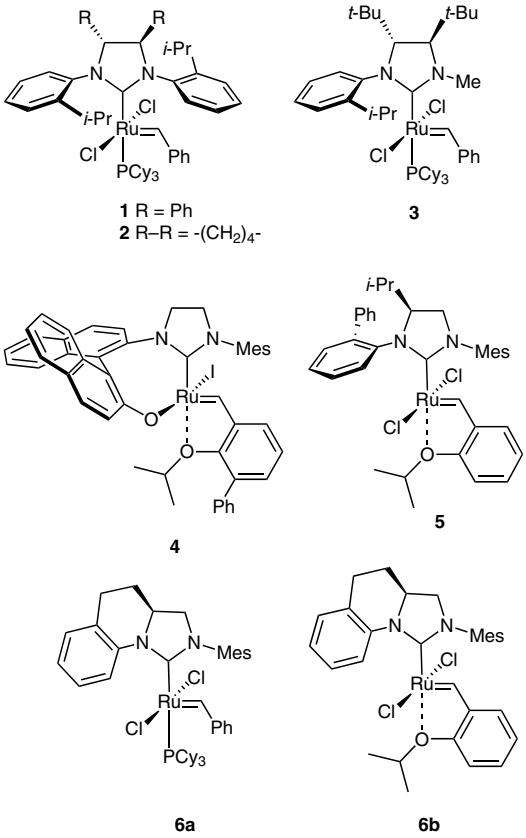
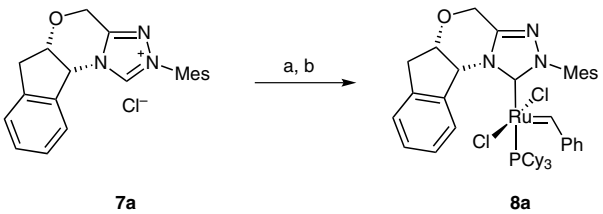


Figure 1 Selected chiral ruthenium metathesis (pre)catalysts

7a with KHMDS followed by addition of Grubbs first-generation catalyst afforded complex **8a** in 60% yield after column chromatography.



Scheme 1 Synthesis of complex **8a**. *Reagents and conditions*: (a) KHMDS, THF, r.t., 15 min; (b) $Cl_2(PCy_3)_2Ru$=CHPh, THF, r.t., 30 min (60% two steps).

We were able to grow a single crystal from Et_2O–MeOH solvent mixture, so the solid-state structure of **8a** has been

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determined (Figure 2; see also Supporting Information for details).

We noted some structural similarities between chiral NHC ligands in compound **8a** and in Blechert's successful catalysts **6a**,**b**.[5b] Having the crystal structure of **8a** in hand, it would have been worth to compare it to the reported structure of catalyst **6a**. Unfortunately, only the crystal structure of **6b** was reported.[5b] Despite **8a** being Grubbs-type and **6b** being a Hoveyda-type complex we decided to compare those two structures anyway.[10] The overlay of **8a** and **6b**[5b] molecules is presented in Figure 3. The coordination geometry of ruthenium atom in **8a** is more distorted in comparison to **6b** i.e. the C1–Ru1–P1 angle is 164.4(1)° and 176.6(2)° for **8a** and **6b**, respectively. Modification of the NHC ligand, e.g. position of chiral centre, leads to the change of its orientation and the C1–N2–C14–C21 torsion angle is equal to −90.1(5)° for **8a** and −50.1(8)° for the corresponding torsion angle of **6b**. Therefore, the observed Ru-H–C agostic interaction in the **6b** precatalyst is not present for **8a** molecule.

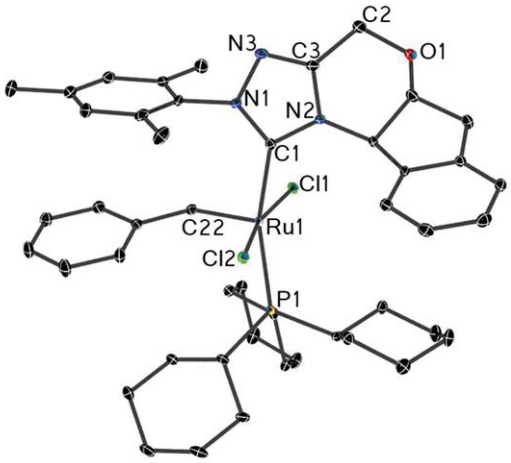


Figure 2 ORTEP representation of complex **8a**. Hydrogen atoms have been omitted for clarity. Thermal ellipsoids are shown at the 50% probability level.

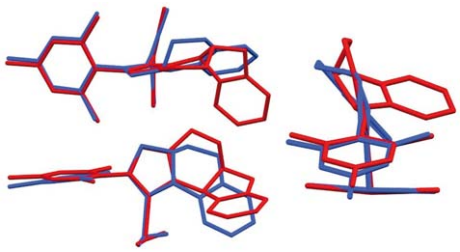
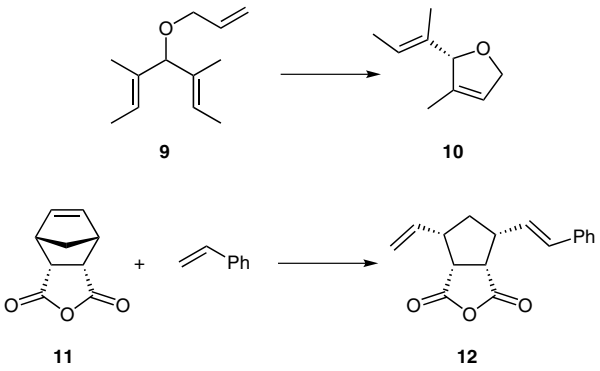


Figure 3 Molecular overlay of **8a** (red) and **6b** (blue). For clarity only Ru-NHC fragment is shown.

ARCM of **9** catalyzed by complex **8a** proceed to full conversion, however only 26% ee was observed for product **10** (Table 1, entry 1). Similarly, AROCM of **11** with styrene (Table 2, entry 1) led to 19% ee only. Bearing in mind the structural similarity to complexes **6a**,**b**, enantioselectivity of reactions catalyzed by **8a** was disappointingly low. It shall be noted, that complex **6a** led to product **12** with 86% ee.[5b] It is known that even minor change in the structure of a NHC ligand could dramatically affect the properties of ruthenium carbene complexes.[11] Unsaturation of NHC backbone and additional nitrogen atom in complex **8a** may explain its different behavior compared to **6a**,**b**.



Scheme 2 ARCM of **9** and AROCM of **11** as model reactions

Table 1 ARCM of **9**[a]

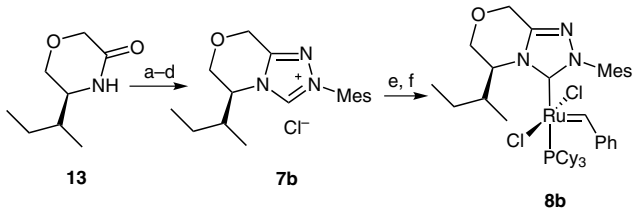
Entry	Catalyst	Conv. (%)[b]	ee (%)[c]
1	**8a**	>95	26
2	**8b**	64	4[e]
3	**8c**[d]	59	9[e]
4	**8d**[d]	85	8
5[f]	**3**	>98[f]	82[f]

[a] Reaction conditions: 5 mol% of Ru complex, CH_2Cl_2, 0.05 M, 40 °C, 3 h.
[b] Determined by GC.
[c] Determined by GC with a chiral column (Agilent® HP-CHIRAL-20B).
[d] Reaction with in situ prepared catalyst.
[e] Excess of opposite enantiomer observed.
[f] See ref. 3.

Although the enantioselectivity of both reactions was disappointingly low with **8a**, we considered this very initial result of being promising. This encouraged us to synthesize analogues of complex **8a**. First, we decided to synthesize a less rigid, yet bulky 1,2,4-triazol-5-ylidene ligand. Starting from morpholinone **13**[12] derived from (*S*)-isoleucine we obtained precursor **7b**[13] which was transformed to catalyst **8b** in 82% yield (Scheme 3).

In the model reactions this catalyst (**8b**) also gave low ee: 4% and 24% (Table 1, entry 2 and Table 2, entry 2). Therefore, after altering the left part of the NHC ligand, and not achieving visible success, we decided to investigate the influence of the flat *N*-aryl substituent modification.

To do so, we used commercially available precursor **7c**[14] bearing *N*-pentafluorophenyl instead of *N*-mesityl group.



Scheme 3 Synthesis of precursor **7b** and complex **8b**. *Reagents and conditions*: (a) Me_3OBF_4, CH_2Cl_2, r.t., 24 h; (b) sat. aq $NaHCO_3$, 0 °C, 30 min, 96% (two steps); (c) $MesNHNH_2$·HCl, HCl cat., MeOH, r.t., 24 h; (d) $(EtO)_3CH$, PhCl, 110 °C, 4 h, 33% (two steps); (e) KHMDS, THF, r.t., 15 min; (f) $Cl_2(PCy_3)_2Ru$=CHPh, THF, r.t., 30 min, 82% (two steps).

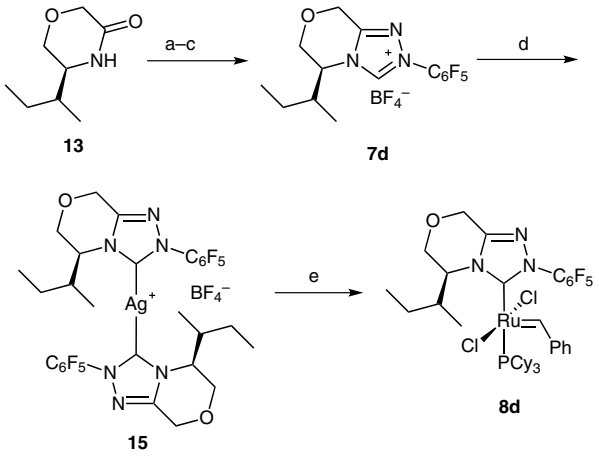
Table 2 AROCM of **11** with Styrene[a]

Entry	Catalyst	Conv. (%)[b]	ee (%)[c]
1	**8a**	>95	19
2	**8b**	>95	24
3	**8c**[d]	17	47[e]
4	**8d**[d]	57	72[e]
5[f]	**6a**	78[f]	86[f]
6[f]	**6b**	83[f]	75[f]

[a] Reaction conditions: 5 mol% of Ru complex, styrene (5 equiv), THF, 0.2 M, 24 °C, 24 h.
[b] Determined by ^{1}H NMR.
[c] Determined by HPLC with a chiral column (Daicel Chiralcel® OJ).
[d] Reaction with in situ prepared catalyst.
[e] Excess of opposite enantiomer observed.
[f] See ref. 5b.

Unfortunately, treatment of **7c** with KHMDS followed by addition of Grubbs first-generation catalyst led to the desired complex **8c** in a low yield, due to incomplete conversion. Silver-NHC complexes are known to be good carbene transfer reagents enabling mild introduction of NHC to other metal complexes.[4d,15] Treatment of **7c** with Ag_2O afforded the silver complex **14** which was easily transformed to the desired ruthenium complex **8c** with full conversion (Scheme 4). However due to low stability, complex **8c** was isolated with significantly lower yield (52%).

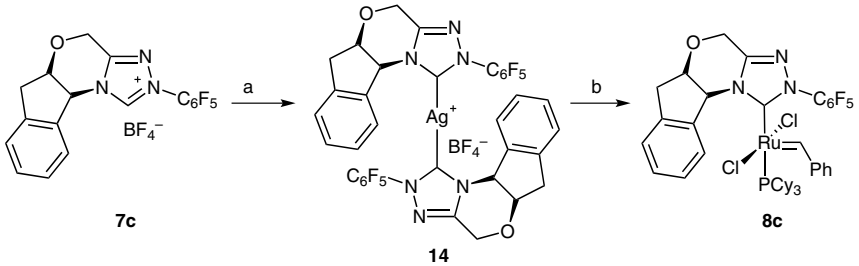
Similarly, starting from morpholinone **13** we obtained precursor **7d**[16] which was transformed to silver complex **15** (Scheme 5). Reaction of **15** with Grubbs first-generation catalyst gave cleanly the expected product with full conversion, but again after column chromatography complex **8d** was isolated with relatively low yield (55%).



Scheme 5 Synthesis of complex **8d**. *Reagents and conditions*: (a) Me_3OBF_4, CH_2Cl_2, r.t., 24 h; (b) $F_5C_6NHNH_2$, CH_2Cl_2, r.t., 24 h; (c) $(EtO)_3CH$, PhCl, 130 °C, 24 h, 72% (three steps); (d) Ag_2O, CH_2Cl_2, r.t., 72 h, 79%; (e) $Cl_2(PCy_3)_2Ru$=CHPh, THF, r.t., 15 min, 55%.

Unfortunately, complexes **8c** and **8d** containing C_6F_5-substituted 1,2,4-triazol-5-ylidene ligand proved to be less stable as compared to their mesityl analogues **8a**,**b**, which makes their isolation and storage problematic. However, since the reactions of silver complexes **14** and **15** with Grubbs first-generation catalyst were completed (according to NMR) within minutes at room temperature, leading cleanly to the expected products, we decided to use in model metathesis reactions in situ prepared complexes **8c** and **8d**, instead of attempting to isolate and purify them.[4d,17]

To our disappointment, in the case of desymmetrization of triene **9**, alteration of the catalysts structure was not successful and the modified catalysts exhibited lower selectivity than the lead complex **8a**. Slightly better results were obtained in AROCM of **11**. Introduction of *N*-pentafluorophenyl to the (pre)catalyst structure led to improvement of selectivity and in the case of complex **8d** product **12** was obtained with 72% ee (Table 2, entry 4); however conversion of the reaction was moderate.



Scheme 4 Synthesis of complex **8c**. *Reagents and conditions*: (a) Ag_2O, CH_2Cl_2, r.t., 72 h, 81%; (b) $Cl_2(PCy_3)_2Ru$=CHPh, THF, r.t., 15 min, 52%.

The change from *N*-mesityl group to *N*-pentafluorophenyl group affects both steric and electronic factors of NHC ligand, but the exact reason for the improvement of stereoselectivity is unclear at the present stage of research. Unfortunately we were unable to obtain a crystal of **8d** which may provide explanation for this observation.

The preliminary results obtained by us show that C_1-symmetric 1,2,4-triazol-5-ylidenes can be used to form chiral Ag and Ru complexes. Less stable Ru complexes **8c** and **8d** can be prepared by mixing two stable metallic precursors and used in situ in asymmetric olefin metathesis. Although observed enantioselectivity levels were lower than those reported for other catalysts described in the literature,[1a,2–5] we hope that further modifications may lead to increasing the catalysts' selectivity. Research in this direction is ongoing in our laboratories and results will be reported in due course.

Acknowledgment

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(10) Both Hoveyda- and Grubbs-type complexes **6a** and **6b** gave very similar results in series of model AROCM reactions, indicating that introduction of chelating 2-isopropoxybenzylidene in place of Cy_3P does not substantially affect the enantioselectivity of the metathesis reactions (cf. ref. 5b).

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(13) **Synthesis of 7b**: (*S*)-5-*sec*-Butylmorpholin-3-one (**13**; 230 mg, 1.46 mmol; see ref. 12) was dissolved in anhyd CH_2Cl_2 (7 mL) and Me_3OBF_4 (259 mg, 1.75 mmol) was added. The mixture was stirred at r.t. for 24 h and then cooled to 0 °C. Sat. aq $NaHCO_3$ (10 mL) was added over 15 min and the mixture was further stirred at r.t. for 30 min. The mixture was extracted with CH_2Cl_2, and the combined organic layers were washed with H_2O and dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure to afford the crude (*S*)-3-*sec*-butyl-5-methoxy-3,6-dihydro-2*H*-1,4-oxazine (239 mg, 96%) as a white solid which was used in the next step without further purification. Mesitylhydrazine hydrochloride (270 mg, 1.46 mmol) was dissolved in anhyd MeOH (6 mL). The crude (*S*)-3-*sec*-butyl-5-methoxy-3,6-dihydro-2*H*-1,4-oxazine (239 mg, 0.48 mmol) was added in one portion followed by HCl (4 M in 1,4-dioxane; 36 µL, 0.20 mmol, 0.100 equiv) and the reaction mixture was stirred at r.t. for 24 h. The solvent was evaporated to give a yellow solid which was dried in high vacuum. The residue was suspended in chlorobenzene (1.5 mL) and triethyl orthoformate (2 mL, 11.7 mmol) was added. The mixture was stirred for 4 h at 110 °C and concentrated in vacuum. After purification by column chromatography (CH_2Cl_2–MeOH = 99:1 to 95:5) the desired product was obtained as an off-white solid (160 mg, 33%).

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(16) **Synthesis of 7d**: (*S*)-5-*sec*-Butylmorpholin-3-one (**13**; 692 mg, 4.40 mmol) was dissolved in anhyd CH_2Cl_2 (10 mL) and Me_3OBF_4 (651 mg, 4.4 mmol) was added. The mixture was stirred at r.t. for 24 h. Pentafluorophenyl hydrazine (872 mg, 4.40 mmol) was added in one portion and the mixture was further stirred for 24 h at r.t. The solvent was evaporated and

residue was dried in high vacuum. Chlorobenzene (5 mL) and triethyl orthoformate (1.8 mL, 11.0 mmol) were added and the mixture was heated to 130 °C for 24 h and then stored overnight in fridge. The precipitated crystals were filtered off and washed with toluene and dried in high vacuum to give the desired product as a white solid (1.40 g, 72%).

(17) **AROCM of 11 with In Situ Prepared Catalyst 8d**: To a solution of bis(tricyclohexylphosphine)benzylidene ruthenium dichloride (8.2 mg, 0.01 mmol, 5 mol%) in anhyd THF (0.5 mL) silver complex **15** (6.2 mg, 0.007 mmol, 3.5 mol%) was added under argon and the reaction mixture was stirred at r.t. for 15 min. After that time the reaction mixture was transferred to a solution of **11** (32.8 mg, 0.2 mmol) and styrene (104.2 mg, 1.0 mmol) in anhyd THF (0.5 mL) and the formed mixture was stirred at 24 °C for 24 h under an argon atmosphere. The reaction was quenched by addition of ethyl vinyl ether and the reaction mixture was concentrated under vacuum. Conversion was determined by ^{1}H NMR while the ee value was determined by HPLC analysis using a chiral column (Daicel Chiralcel® OJ).

