Amino acids as chiral anionic ligands for ruthenium based asymmetric olefin metathesis†

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Since its universal recognition in 2005, the field of olefin metathesis in organic synthesis has continued its phenomenal development in many aspects, such as: Z-selectivity, latency, synthesis of sterically hindered alkenes, aqueous based metathesis, etc. Asymmetric olefin metathesis, as in ACM (asymmetric cross metathesis), ARCM (asymmetric ring closing metathesis) and AROCM (asymmetric ring opening cross metathesis), provides accessible pathways for the production of some elusive chiral products. The first examples of asymmetric olefin metathesis were presented by Schrock and Grubbs et al. using chiral molybdenum complexes. However, the applicability of these complexes was reduced by their sensitivity towards air and water and their low tolerance for a variety of functional groups. More recent studies have produced more stable molybdenum catalysts and significantly advanced the field of molybdenum asymmetric olefin metathesis. The first examples of chiral ruthenium complexes date back to 2001 and new asymmetric catalysts are still being produced today. Notwithstanding the efficiency observed for these chiral complexes, they all require intricate and expensive syntheses of chiral NHC ligands. In light of this, the exploration of straightforward and low cost synthesis protocols of novel functional group tolerant ruthenium pre-catalysts for asymmetric metathesis has remained highly desirable. Moreover, it has been proven over time that there is no “silver bullet” in olefin metathesis reactions and different substrates and conditions many times require catalyst optimization. Thus, the ability to produce tunable chiral catalysts is also a sought after goal. Even though in most of the commonly used ruthenium alkylides the anionic positions are occupied by chloride ligands, the introduction of different halides and pseudo-halides has been extensively studied in this area. Fine-tuning of the anionic ligands can result in different reactivity and selectivity of the pre-catalysts.

Herein, we report on the synthesis of several ruthenium-based olefin metathesis complexes bearing amino acids as chiral anionic ligands and study their efficiency in asymmetric olefin metathesis reactions. The complexes are produced from the most ubiquitous chiral entities in a facile and economical manner, presenting highly tunable options to study this family of asymmetric ruthenium pre-catalysts.

Amines are strong σ-donor ligands capable of coordination to the ruthenium center and thus need to be protected when introduced to ruthenium alkylidene solutions. Accordingly, Boc(tert-butyloxycarbonyl) N-substituted amino acids were chosen as starting materials. The protected amino acids were converted to their silver carboxylate salts to ensure complete substitution of both chlorides and 2.1 equivalents of the corresponding silver salts were introduced to ruthenium alkylidene solutions. Accordingly, Boc(tert-butyloxycarbonyl) N-substituted amino acids were chosen as starting materials. The protected amino acids were converted to their silver carboxylate salts to ensure complete substitution of both chlorides and 2.1 equivalents of the corresponding silver salts were introduced to a THF solution of a commercially available Hoveyda–Grubbs 2nd generation complex (Table 1). Interestingly, the use of methylene chloride as the solvent medium led to unsatisfactory results and decomposition of the amino acid ruthenium complexes. Visibly, complexes in methylene chloride solution significantly decomposed after 24 hours, affording an aldehyde by-product and exposing the fragility of these complexes compared to their dichloro counterparts (see ESI†). Filtration of the precipitated silver chloride and evaporation of the solvent afforded the products as deep purple solids. Using this straightforward protocol, complexes Ru-G, Ru-A, Ru-L and Ru-F bearing Boc protected glycine, alanine, leucine and phenylalanine, respectively, were prepared. All complexes were obtained in good yields and were duly characterized by NMR spectroscopy, HRMS and specific rotation measurements (Table 1 and ESI†). As an exception, the use of the Boc-valine and Boc-proline amino acids produced a mixture of the starting material.

† Electronic supplementary information (ESI) available: Synthesis, characterization and activity of all new complexes, and CIF file for Ru-G. CCDC 1037063. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5cc00052a

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Table 1  Synthesis of ruthenium complexes bearing amino acid anionic ligands

| Complex        | R substituent | Yield (%) | Benzylidene hydrogen^a (ppm) | Specific rotation^b (°) |
|----------------|--------------|-----------|-----------------------------|------------------------|
| Hoveyda-Grubbs II | —            | 16.72     | 0.00                        |                         |
| Ru-G           | H            | 94        | 17.99                       | 0.00                   |
| Ru-A           | CH3          | 95        | 17.62                       | +38.3                  |
| Ru-L           | CH(CH3)2     | 77        | 17.58                       | −18.2                  |
| Ru-F           | CH3Ph        | 87        | 17.73                       | −37.5                  |
| Ru-DA          | CH3          | 78        | 17.61                       | −38.5                  |

Reaction conditions: THF, 37 °C, 3 hours. ^a C6D6, 400 MHz, for full NMR spectra see ESL. ^b Specific rotation measured in toluene at [a]D23.

Table 2  AROCM and ARCM with chiral Ru pre-catalysts

| Entry | Substrate | Product | Catalyst         | Conversion^a [%] | eeb^b [%] |
|-------|-----------|---------|------------------|------------------|-----------|
| 1     | 1         | 3       | Hoveyda-Grubbs II | 100              | 0         |
| 2     | Ru-G      | —       | —                | 100              | 0         |
| 3     | Ru-A      | —       | —                | 100              | 4         |
| 4     | Ru-DA     | —       | —                | 100              | 4         |
| 5     | Ru-F      | —       | —                | 100              | 4         |
| 6     | 2         | 4       | Hoveyda-Grubbs II | 100              | 0         |
| 7     | Ru-G      | —       | —                | 83               | 0         |
| 8     | Ru-F      | —       | —                | 93               | 0         |
| 9     | Ru-L      | —       | —                | 100              | 12        |
| 10    | Ru-A      | —       | —                | 100              | 20        |
| 11    | Ru-DA     | —       | —                | 100              | 20        |

AROCM conditions: 8.0 mol% catalyst loadings, 13.0 equivalents of styrene, 55 mM substrate in THF, 37 °C, 2 hours. ARCM conditions: 8.0 mol% catalyst loadings, 55 mM substrate in THF, 37 °C, 2 hours. ^a Conversion was monitored by GC-MS. ^b ee was determined by HPLC (Reprosil chiral-NR, 8 μm, 150 × 4.5 mm). ^c 2.5 mol%, ‡ 7.0 mol%.

2 catalyzed by Ru-DA readily provided excess of the opposite enantiomeric product to that obtained by the use of Ru-A (Table 2, entries 10 and 11) as shown by the different chiral HPLC chromatograms (see ESIF). For both metathesis reactions we expected increased ee as the size of the substituent of the amino acid increased (i.e. highest ee for Ru-F); yet Table 2 displays the opposite trend. This seems to imply that a fine balance between steric hindrance and electronic effects is required in order to obtain satisfactory asymmetric induction. While greater steric stress in the asymmetric environment could contribute to higher enantioselectivity, we hypothesized that steric hindrance may also lead to enhanced ligand dissociation, leading to a detrimental outcome. Ligands at the anionic positions in Hoveyda-Grubbs type complexes are known for their lability and dynamic nature, and were shown in solution to dissociate as a part of a degenerate ligand exchange.19 Both reduced complex stability and ligand dissociation may be the cause for the low enantioselectivities observed in Table 2.

In order to study the specific lability of the amino acid ligands used, disproportionation of Ru-A and Ru-F in the presence of Boc-glycine silver salt (Scheme 1) was monitored by 1H-NMR. Qualitative inspection of the carbene region disclosed a faster exchange of the Boc-phenylalanine ligand by the Boc-glycine ligand, compared to the Boc-alanine ligand. This observation falls in line with our assumption that greater steric stress in the system facilitates ligand dissociation. Since the chiral induction in our system originates from the anionic ligand, greater ligand

Fig. 1  ORTEP representation (50% probability ellipsoids) of complex Ru-G. Hydrogen atoms were omitted for clarity.

along with mono- and di-substituted ruthenium complexes, probably due to the higher steric congestion introduced by the isopropyl and pyrrolidine side groups (see ESIF). Notably, while complex Ru-F has a specific rotation of −37.5°, the specific rotation of Boc-phenylalanine (Boc-phenylalanine was the only protected amino acid used soluble in toluene) was measured to be +27.6°, strongly suggesting that optical rotation of polarized light is caused by the complex itself and not by dissociated amino acid in solution. Complex Ru-G was also characterized by single crystal X-ray spectroscopy, showing the typical η5 hapticity for one of the carbonate ligands (Fig. 1).

The catalytic efficacy of complexes Ru-G, Ru-A, Ru-L and Ru-F was tested in ARCM and AROCM benchmark reactions.7b The initial results showed excellent conversions for AROCM of norbornene 1 and ARCM of triene 2 (Table 2), but with very poor enantioselectivities. Alanine complex Ru-A afforded the highest enantioselectivity with just 20% ee. Lowering the temperature to 0 °C improved the ee to 27%, yet significantly reduced the conversion.

An advantage of this methodology is that amino acids are readily available in their mirror-image forms and thus hold a valuable key for major product selection. To demonstrate the ease with which a specific enantiomer may be obtained, readily available N-Boc protected α-alanine was used to synthesize Ru-DA under the same conditions described previously. Ru-DA displayed NMR spectra identical to those of Ru-A and opposite specific rotation (Table 1). As expected, asymmetric ring closing of triene

Scheme 1

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[Image of complex Ru-G]

[Diagram of metathesis reactions]
dissociation can severely hamper the enantioselectivity obtained. In order to achieve enantioselectivity without a chiral NHC ligand, it is reasonable to assume that both chiral anionic ligands must be associated with the ruthenium center during the stereochemistry determining step. In related work, Grela et al. probed the asymmetric efficiency of a chiral at metal ruthenium pre-catalyst. The complex, bearing two, not labile, achiral anionic ligands (trifluoroacetate and iodide ligands), was isolated in its optically pure form. Lack of enantioselectivity in this system was explained by a fast racemization mechanism of the propagating species and underlined the need for a permanent asymmetric induction derived directly from the ligands for asymmetric olefin metathesis.

To further support the hypothesis that ligand lability was hampering enantioselectivity, an ARCM reaction catalyzed by Ru-A was carried out in the presence of excess of Boc-alanine silver salt (Table 3, entries 1 and 2). To our satisfaction, an increase in ee from 20% to 34% was observed by this protocol (alongside increased isomerization of the substrate). Continuing with this line of reasoning, the reaction was repeated in a less polar solvent to inhibit ligand dissociation. Indeed, changing the solvent from benzene to THF increased the ee from 20% to 34% was observed by this protocol. To the best of our knowledge, this is the first report of utilizing such simple choice of the appropriate amino acid symmetry and an order to achieve enantioselectivity without a chiral NHC ligand, it is reasonable to assume that both chiral anionic ligands must be

| Entry | Solvent | Additive $^{a}$ | Conversion $^{b}$ [%] | ee $^{c}$ [%] |
|-------|---------|-----------------|-----------------------|-------------|
| 1     | THF     | —               | 100                   | 20          |
| 2     | THF     | Ala-OAg         | 99$^{d}$              | 34          |
| 3     | Benzene | —               | 92$^{d}$              | 44          |
| 4     | Benzene | Ala-OAg         | 63$^{d}$              | 56          |

ARCM conditions: 8.0 mol% catalyst loadings, 55 mM substrate in solvent, 37 $^\circ$C, 2 hours. $^{a}$ 40 mol% with respect to Ru-A. $^{b}$ Conversion was determined by GCMS. $^{c}$ ee was determined by HPLC (Reprosil chiral-NR, 8 $\mu$m, 150 x 4.5 mm). $^{d}$ Accompanied by cycloisomerization products.

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