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Short communication

Asymmetric transfer hydrogenation of ketones by N,N-containing quinazoline-based ruthenium(II) complexes

Cigdem Kucukturkmen [a], Ahmet Agac [b], Aysel Eren [b], Idris Karakaya [c], Mehmet Aslantas [b], Omer Celik [d], Sabri Ulukanli [c], Semistan Karabuga [b,*]

[a] Department of Chemistry, Faculty of Science and Letters, Kilis 7 Aralık University, 79100 Kilis/Turkey
[b] Department of Chemistry, Faculty of Science and Letters, Kahramanmaras Sutcu Imam University, 46100 Kahramanmaras, Turkey
[c] Department of Chemistry, Faculty of Science and Letters, Osmaniye Korkut Ata University, 80000 Osmaniye, Turkey
[d] Department of Chemistry, Faculty of Science and Letters, Dicle University, 21280 Diyarbakır, Turkey

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ABSTRACT

The novel set of quinazoline-based chiral ligands was synthesized starting from optically pure amino acids. Coordination with $RuCl_2(PPh_3)$dppb gave ruthenium(II) N-heterocyclic complexes **4b–d**. The structure of complex **4b** was fully illuminated by X-ray crystallography. The steric environment of these chiral ruthenium complexes **4b–d** was evaluated in asymmetric transfer hydrogenation (ATH) of prochiral ketones in the presence of NaO^iPr by using 2-propanol as the hydrogen source and solvent. The resultant catalytic system can achieve very good enantioselectivities (up to 91%) and high yields (up to 99%).

1. Introduction

Asymmetric transfer hydrogenation (ATH) of carbonyl compounds catalyzed by transition metal complexes is a desirable method to prepare optically active alcohols which are useful intermediates in the synthesis of pharmaceuticals and agrochemicals. In recent years, many studies have been conducted in this area seeking to identify an easily handled hydrogen source, mild reaction conditions and mainly low cost. In spite of these advances, ongoing studies still work to identify a better catalytic system [1,2]. Currently, state of the art ATH chemistry is mediated by metal complexes of Ru, Ir, and Rh. In 1995, a seminal contribution to the field was achieved by Noyori using a chiral Ru–NH catalyst system that exhibited very high activity in the ATH reaction of ketones [3,4] Since this initial contribution, numerous catalytic system [5,6] using NN [7–13], NNN [14], CNN [15,16], PNN [17], NO [18], NNO [19] etc., types of ligands have been prepared (Fig. 1). In particular Wills and co-workers have used ruthenium complexes based on optically pure *N*-tosylated-1,2-diphenylethane-1,2-diamine **1** (TsDPEN) in ATH reactions [20,21]. *N*-Heterocyclic compounds such as pyridine **2** have been frequently employed as ligands in catalytic reactions, largely due to their boosted stability and convenient structure for coordination chemistry. Various ruthenium and osmium catalysts including primary amine **3** and pyridyl [22–24] or quinolinyl [22,24,25] donor groups have been prepared for ATH of carbonyl compounds with high catalytic activities by Baratta and co-workers. Similar types of ruthenium complexes such as pyrazolyl [25], oxazolinyl [26], imidazolyl [22,27 ,28] and *N*-heterocyclic carbene [29] have been largely studied in ATH reaction in recent years by several research groups.

In our previous report, we developed the quinazoline-based ruthenium complex [30] **4a** from glycine. Very good conversions were obtained by examining acetophenone and its derivatives in the transfer hydrogenation reaction. Through that study, we performed ATH reaction for catalytic activities of ruthenium complexes **4b–d** based on the chiral quinazolines **8b–d** which were synthesized from optically pure L-alanine **5b**, L-valine **5c** and L-*t*-leucine **5d**.

2. Results and discussion

The optically pure chloroquinazolines **6b–d** (Scheme 1) were prepared from readily available L-amino acids in accordance with our previous report [31]. The chloroquinazolines **6b–d** were carried out via coupling reactions with phenyl boronic acid in the presence of catalytic amount of $Pd(PPh_3)_4$ at reflux under N_2 atmosphere and then the Boc group was deprotected with TFA to afford the 4-phenylquinazolines **8b–d** with moderate yields in two steps (52–68%).

* Corresponding author.
E-mail address: semistan@ksu.edu.tr (S. Karabuga).

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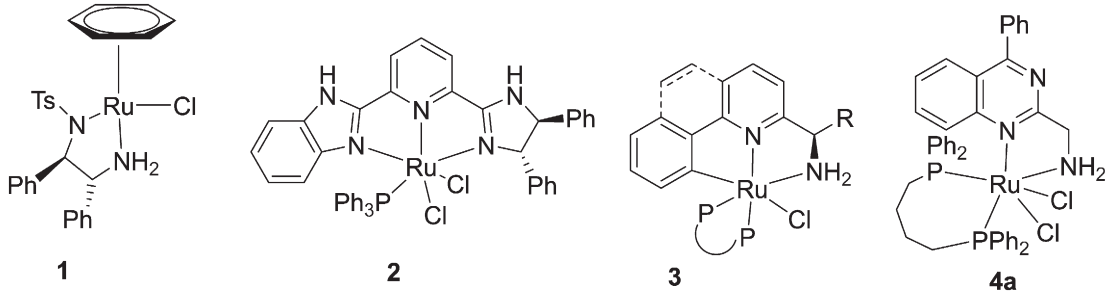
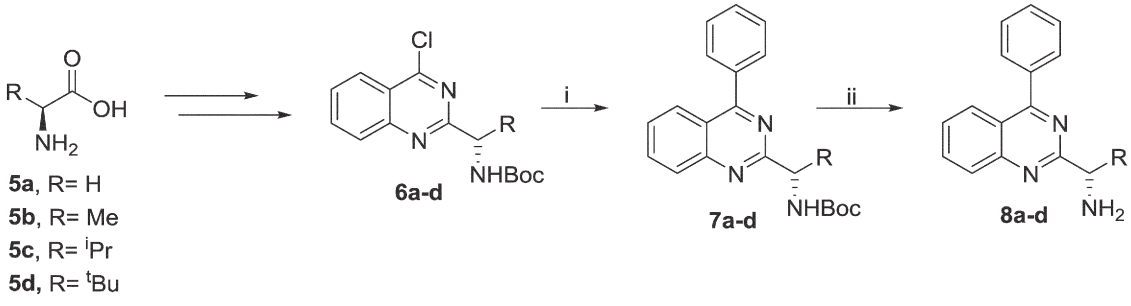


Fig. 1. Several ligands coordinated with ruthenium.

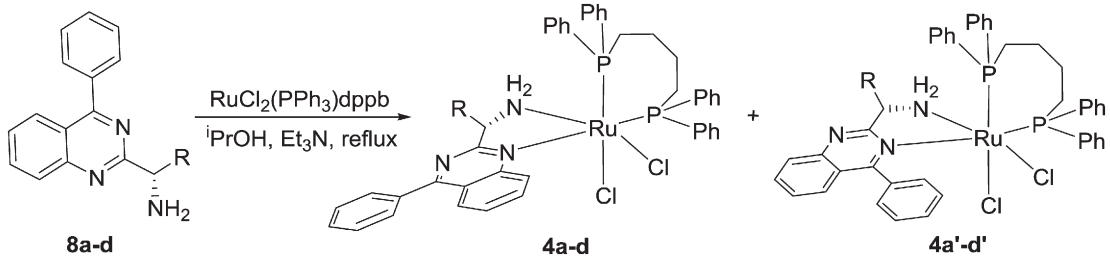
The 4-phenylquinazolines **8b–d** were then treated with $RuCl_2(PPh_3)$dppb in the presence of Et_3N and ^iPrOH as a solvent at reflux temperature for 3 h, which resulted in the formation of the ruthenium complexes **4b–d** (Scheme 2). All of these ruthenium complexes were structurally characterized using NMR, HRMS, and FT-IR. Furthermore, to conclusively determine the structure, a single crystal X-ray diffraction analysis was performed on **4b**. In our previous report [30], two isomers **4a–a′** had been detected in the ratio of about 4:1 from NMR analysis when ruthenium complexes were prepared with the quinazoline **8a**. Density functional theory (DFT) calculations on this complex predicted this observation showing that the electronic energy values predicted **4a** as more stable than **4a′**. As anticipated from this earlier work, two types of ruthenium complexes were obtained by treating with $RuCl_2(PPh_3)$dppb and optically pure quinazolines **4bd** in this study.

The ^1H NMR spectrum of complex **4b,4b′** shows two doublets at 10.44 and 10.11 ppm which suggest the formation of two complexes in a ratio of 5.2:1. This result can also be observed for several signals at 6.66, 6.40 and 1.34 ppm of major complex **4b** and against signals at 6.71, 6.44 and 1.38 ppm of minor complex **4b′** with the same ratio. Further ^{31}P NMR verified this proposed structure with two doublets at 52.65 and 40.53 ppm [^2J (P,P) = 39.1 Hz] for the **4b** and similarly two doublets 56.23 and 43.04 ppm [^2J (P,P) = 41.3 Hz] for the **4b′** as well. The reaction scaled up and rinsed several times with ethyl ether and then petroleum ether as distinct from the first synthesis. Thereupon, the minor signals which belong to complex **4b′** observed both in ^1H and ^{31}P NMR spectra disappeared and the major complex **4b** was crystallized from CH_2Cl_2 for single X-ray analysis.

The ORTEP [32] drawing of the molecule indicating atom numbering scheme with thermal ellipsoids at %30 probability is shown in Fig. 2. (Crystal and experimental data of complex **4b** are displayed in Table S1 and selected bond lengths and angles are listed in Table S2 in supporting information.) The PARST [33] and PLATON [34] programs were used for geometrical calculation and conformational features of the title compound **4b** ($C_{44}H_{43}Cl_2N_3P_2Ru$). In the title complex **4b**, the ruthenium center is six-coordinated by two P, two Cl and N atoms of the quinazoline ligand **8b**. The groups of N(1), N(3), P(2) and Cl(1) atoms form a square planar arrangement in equatorial plane with the maximum deviation from its best plane of −0.026(2) Å for P(2) atom, while the distorted octahedral geometry is completed by the P(1) and Cl(2) atoms which are in the axial positions. The quinazoline group **8b** is coordinated to Ru atom in order to form a five-membered RuC(2)N(2) ring causes for narrowing the angle of N(1)–Ru(1)–N(3) [(72.7(2)°] considerably and shortening N–N outer distance in the square like plane. The distorted octahedron geometry



Scheme 1. Synthesis of 4-phenylquinazoline amines **8b–d**, reagents and conditions: (i) $PhB(OH)_2$, Na_2CO_3, $Pd(PPh_3)_4$, EtOH/DME, reflux, 2 h; (ii) TFA, CH_2Cl_2, rt., 6 h.



Scheme 2. Synthesis of complexes **4a–d**, reagents and conditions: (a) $RuCl_2(PPh_3)$dppb, Et_3N, ^iPrOH, reflux, 3 h.