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N-Heterocyclic Carbene−Ruthenium Complexes for the Racemization of Chiral Alcohols

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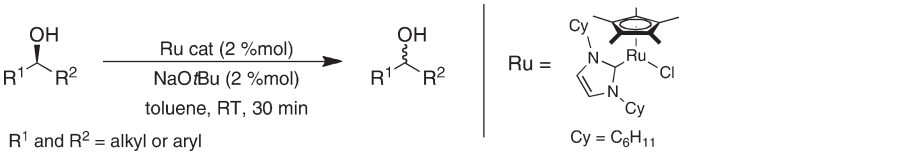

The activity of well-defined 16-electron ruthenium complexes bearing an *N*-heterocyclic carbene ligand in the racemization of chiral alcohols is reported. Mechanistic considerations are also presented.

Introduction

Racemization reactions are intricate components of protocols making use of chiral synthons in synthesis.[1] More specifically, in the field of dynamic kinetic resolution (DKR), a racemization catalyst is directly introduced into a kinetic resolution reaction, allowing the complete conversion of the racemic substrate into an enantiomerically pure derivative.[2] Nevertheless, the development of new catalysts able to racemize substrates under mild conditions remains a challenge. The best performing catalysts enabling alcohol racemization[3] are based on ruthenium,[4,5] and among these, the Shvo catalyst (**A**, Figure 1)[6,7] has been successfully applied to racemization reactions as part of DKR processes as disclosed by Bäckvall.[8] The activity of the dimeric **A** involves, upon thermal activation, the liberation of two ruthenium species: an 18-electron ruthenium(II) complex **A1** and a 16-electron ruthenium(0) complex **A2** (Figure 1).[6] Transfer dehydrogenation of a chiral alcohol by **A2** yields the corresponding ketone which then undergoes a non-stereoselective transfer hydrogenation reaction mediated by **A1**, leading to the corresponding racemized alcohol.[9] Park et al. have developed a family of 18-electron ruthenium(II) complexes analogous to the **A1** monomer of the Shvo catalyst and applied them to racemization in DKR reactions (**B**, Figure 1).[10] Bäckvall has reported[11] a remarkable 18-electron ruthenium(II) catalyst analogue of **A1** (**C**, Figure 1) able to racemize alcohol at rt within minutes.[12] Racemization catalysts derived from the Shvo catalyst are based on monomer

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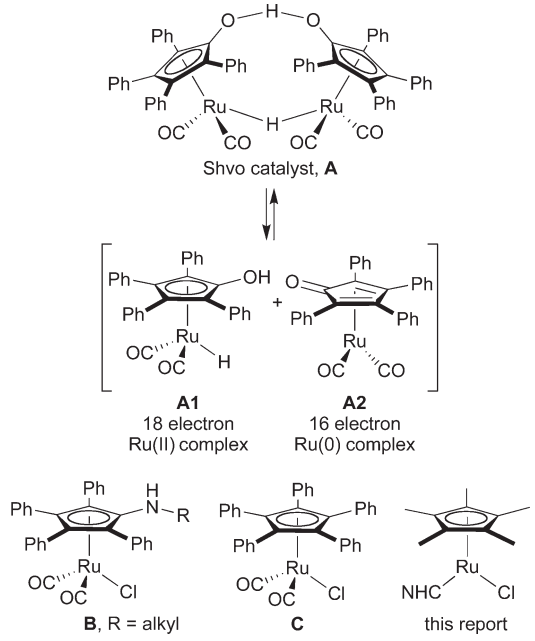


FIGURE 1. Ruthenium complexes involved in alcohol racemization.

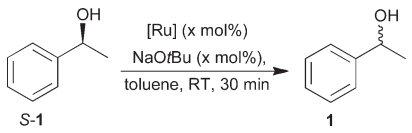
A1, and to the best of our knowledge, no examples of racemization reactions mediated by well-defined 16-electron ruthenium complexes similar to **A2** have been reported.[13]

Herein, we report the use of a family of well-defined 16-electron ruthenium catalysts in chiral alcohol racemization (Figure 1). These well-defined ruthenium(II) complexes represent rare examples of the use of *N*-heterocyclic carbene (NHC) ligands in racemization reactions.[14,15]

Results and Discussion

The study begins with the working hypothesis that if 16-electron complexes are involved in the racemization reactions mediated by the Shvo catalyst, as a 16-electron is formed upon scission of the dimeric Shvo catalyst, then maybe simple well-defined complexes adopting the 16-electron configuration might themselves exhibit catalytic activity. Having examined the thermochemistry and synthesis of well-defined 16-electron complexes in the past,[16] the family of ruthenium complexes examined was the one evolving from the simple tetramer $[Cp^*RuCl]_4$ (**D**)[17] scission reactions with sterically demanding ligands. The model reaction examined is the racemization of (*S*)-1-phenylethanol (*S*-**1**) (Table 1). Whereas the use of **D** led to 38% racemization after 30 min

TABLE 1. Optimization of the Racemization Reaction Conditions[a]



entry		catalyst	mol %	conc (M)	rac[b] (%)
1	**D**	$[Cp^*RuCl]_4$	5[c]	0.1	38
2	**E**	$[Cp^*Ru(P\text{-}i\text{-}Pr_3)Cl]$	5	0.1	80
3	**F**	[Cp*Ru(IAd)Cl]	5	0.1	29
4	**G**	[Cp*Ru(IPr)Cl]	5	0.1	44
5	**H**	[Cp*Ru(IMes)Cl]	5	0.1	13
6	**I**	[Cp*Ru(ICy)Cl]	5	0.1	>99
7	**I**	[Cp*Ru(ICy)Cl]	2	0.5	>99

[a]Reaction on 0.25 mmol of alcohol. [b]Racemization determined by chiral stationary-phase HPLC, average of two runs. [c]1.25 mol % of tetramer was used.

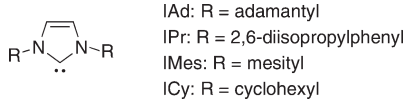


FIGURE 2. *N*-Heterocyclic carbenes (NHC) used in this study.

(Table 1, entry 1), which was in itself promising, the use of $[Cp^*Ru(P^iPr_3)Cl]$(**E**)[18] increased the racemization yield to 80% (Table 1, entry 2). The first attempts using NHC-bearing ruthenium catalyst employing *N*,*N*′-di(adamantyl)imidazol-2-ylidene (IAd, complex **F**)[19] as a ligand were disappointing (Table 1, entry 3), but the use of the less sterically hindered NHC *N*,*N*′-2,6-di-*iso*-propylphenylimidazol-2-ylidene (IPr, complex **G**)[19] increased the racemization to 44% (Table 1, entry 4). Surprisingly, *N*,*N*′-dimesitylimidazol-2-ylidene (IMes) exhibited low reactivity (complex **H**,[20] Table 1, entry 5), but *N*,*N*′-dicyclohexylimidazol-2-ylidene (ICy, complex **I**)[19] led to complete racemization within 30 min, highlighting a dramatic ligand effect (Table 1, entry 6).

Interestingly, by increasing the reactant concentration, good conversions could be achieved with a reduced catalyst loading of 2 mol % (Table 1, entry 7).

In order to rationalize the ligand effect observed, we examined the steric and electronic properties of the NHCs involved in this study (Figure 2). Electronic properties are gauged by analysis of the infrared bands associated with the CO stretching in the corresponding $Ni(CO)_3(NHC)$ complexes, which are reported in Table 2.[19] For the $Ni(CO)_3$-(IAd) IR data, the carbonyl stretching frequency was determined by interpolation of an existing relationship.[21,22] The steric properties of the NHC ligands were quantified from their percent buried volume ($\%V_{Bur}$).[23] Some of these values have been previously reported.[24] Here, they were calculated

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TABLE 2. Electronic and Steric Properties of the Involved NHC

entry	NHC	ν_{CO}[a] (cm^{-1})	$\%V_{Bur}$[b]	*r* parameter[a]	rac (%)
1	IAd	2045.8	34.0	8.0	29
2	IPr	2051.5	31.2	1.8	44
3	IMes	2050.7	31.4	1.5	13
4	ICy	2049.6	25.6	1.6	>99

[a]Dertermined in $Ni(CO)_3(NHC)$. [b]Determined in [Cp*Ru(NHC)Cl] complexes using Samb*V*ca.

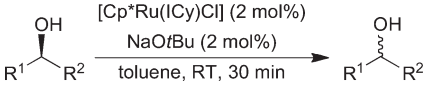
using the crystallographically determined Ru−(NHC) bond distance and the Samb*V*ca Web-based application (see the Supporting Information).[25] We also compared the steric properties of those NHCs with the newly defined *r* parameter, which is a measure of the direct repulsive interactions between the NHC and the carbonyl ligands of $Ni(CO)_3$-(NHC).[22]

The steric hindrance of the NHC ligands tested appears to play a major role in the racemization efficiency. The ligand steric properties ($\%V_{Bur}$) clearly highlight that the smallest NHC (i.e., ICy, Table 2, entry 4) is the most efficient ligand in racemization reaction among the NHCs evaluated. The NHCs examined are all excellent σ donors and the electronic property variations observed, which are small, do not satisfyingly explain the relative reactivity of ICy versus that of its larger congeners (Table 2). A similar trend in NHC steric vs electronic properties has been observed in the ruthenium-catalyzed oxidation of alcohols to amides[26] and in iridium-NHC-based transfer hydrogenation reactions.[27] No correlation between the *r* parameter and the catalyst activity is apparent.

With the optimized racemization conditions in hand, a short reaction scope was next examined. As mentioned, (*S*)-phenylethanol (*S*-**1**) was converted to the racemic form of the alcohol within 30 min with an isolated yield of 92% (Table 3, entry 1). (*S*)-2-Naphthylethanol (*S*-**2**) was also effectively racemized (Table 3, entry 2). For (*R*)-*p*-chlorophenylethanol (*R*-**3**), 90% racemization was reached with a good yield (Table 3, entry 3), suggesting a noticeable detrimental influence of this electron-withdrawing group on the reaction. Heating the reaction for 2 h at 50 °C was required to obtain 55% racemization of the sterically hindered and electron-poor (*S*)-*o*-bromophenylethanol (*S*-**4**, Table 3, entry 4). More remarkably, the aliphatic (*S*)-octan-3-ol (*S*-**5**) was racemized within 30 min (Table 3, entry 5), whereas in the case of its electron-poor counterpart (*S*)-3-benzyloxypropan-2-ol (*S*-**6**), 67% racemization was reached but heating was required (Table 3, entry 6).

Focusing on the reaction mechanism, the ruthenium *tert*-butoxide complex, obtained by treatment of [Cp*Ru(ICy)Cl] with NaO-*t*-Bu, is believed to be an intermediate in the racemization reaction (Scheme 1). NMR data are consistent with such an intermediate as is clearly shown by the resonances attributed to the novel alkoxide species in Figure 3 (top).[27a]

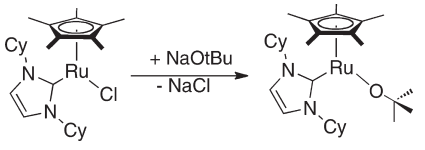
TABLE 3. Scope of the Racemization Reaction[a]



Entry	Substrate	Rac. (%)[b]	Yield (%)[c]
1	*S*-**1**	>99	92
2	*S*-**2**	96	92
3	*R*-**3**	90	89
4[d]	*S*-**4**	55	>99
5	*S*-**5**	98[e]	85
6[d]	*S*-**6**	67	>99

[a]Reaction conditions: 1.00 mmol of substrate; catalyst loading, 2 mol %; base, 2 mol %; concentration, 0.5 M. [b]Racemization determined by chiral stationary-phase HPLC, average of two runs. [c]Isolated yields after flash chromatography, average of two runs. [d]Reaction mixture stirred 2 h at 50 °C. [e]Determined by chiral HPLC after conversion to the corresponding benzyl ester.

SCHEME 1. Formation of the Ruthenium *tert*-Butoxide Complex I1



I **I1**

Alcohol racemizations mediated by catalysts **A**, **B**, or **C** are proposed to proceed through the oxidation of the chiral alcohol to the corresponding ketone and then its reduction back to the alcohol in a non-stereoselective manner.[9a,10b,28b] This oxidation−reduction pathway can be achieved through an "outer sphere" or through an "inner sphere" pathway. In the so-called "outer sphere" path, the intermediate ketone is

(25) https://www.molnac.unisa.it/OMtools/sambvca.php. See also: Poater, A.; Cosenza, B.; Correa, A.; Giudice, S.; Ragone, F.; Scarano, V.; Cavallo, L. *Eur. J. Inorg. Chem.* **2009**, 1759−1766.

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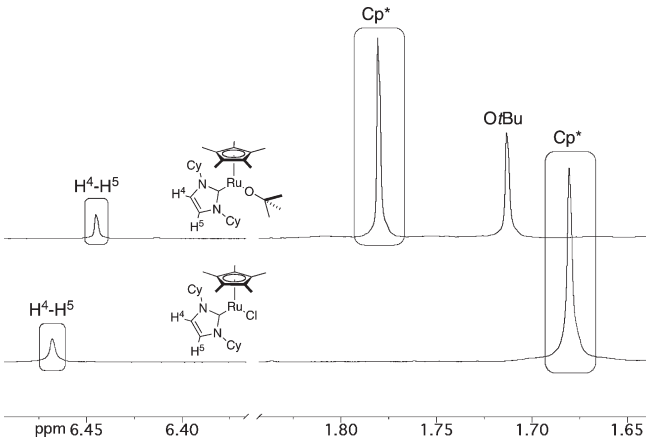


FIGURE 3. ^{1}H NMR data for Cp*Ru(ICy)Cl (bottom) and Cp*Ru(ICy)(O-*t*-Bu) (top).

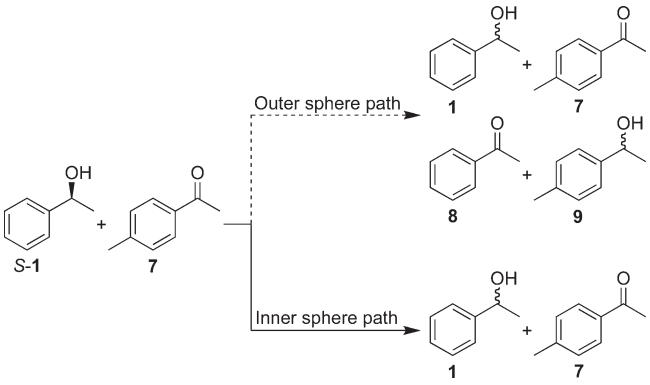


FIGURE 4. Experiment supporting the "inner sphere" pathway.

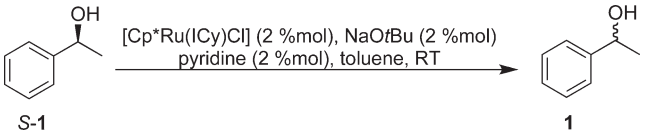
not coordinated to the metallic species, whereas in the so-called "inner sphere" path, the intermediate ketone is not released in the reaction mixture but stays coordinated to the metal catalyst.[29] To assign the reaction pathway of the racemization reaction mediated by the 16-electron ruthenium species examined here, we conducted a racemization experiment on a 1:1 mixture of *S*-**1** and *p*-tolyl methyl ketone **7** (Figure 4).

While an "outer sphere" mechanism would lead to the formation of four compounds in stoichiometric amounts, an "inner sphere" mechanism would only allow for the racemization of the alcohol. The ketone would remain a spectator of the reaction.[28b] In our case, this reaction led to the complete racemization of *S*-**1** within 30 min and without formation of any byproducts. The ketone remained unreacted, and the alcohol/ketone ratio was maintained constant during the process, ruling out an "outer sphere" mechanism.

We next examined whether the vacant site on the ruthenium center, i.e., formation of a 16-electron complex form, was compulsory to catalyze the racemization or whether the reaction could proceed through a $\eta^5 \rightarrow \eta^3$ ring slippage, as possibly involved with the 18 electron ruthenium complexes.[28c] Casey et al. reported that addition of 1 equiv of pyridine on a 16-electron ruthenium complex leads to the incorporation of the pyridine into the coordination sphere of the metal center,

(29) Samec, J. S. M.; Bäckvall, J.-E.; Andersson, P. G.; Brandt, P. *Chem. Soc. Rev.* **2006**, *35*, 237–248.

TABLE 4. Addition of Pyridine to a Racemization Reaction



entry	rac after 15 min[a] (%)	rac after 30 min[a] (%)
1[b]	31	33
2[c]	55	60

[a]Racemization determined by chiral stationary phase HPLC, average of two runs. [b]Addition of pyridine concomitant with the alcohol. [c]Addition of pyridine after 2 min of reaction.

forming an 18-electron ruthenium complex.[30] We investigated the consequences of the addition of pyridine into the reaction mixture (Table 4).

Addition of pyridine into the reaction mixture concomitant with the addition of the chiral alcohol led to a dramatic decrease of the racemization rate over the time (Table 4, entry 1). Moreover, addition of pyridine after the beginning of the racemization reaction resulted in almost halting the racemization process (Table 4, entry 2). This indicates that the vacant site on the ruthenium center is essential for the reaction to proceed. We strongly favor the simple occupation of pyridine to the existing vacant site rather than the pyridine binding a vacant site generated by $\eta^5 \rightarrow \eta^3$ ring slippage which would be a much higher energy process.

The reaction mechanism for the racemization mediated by complex **B** is proposed to involve a metal hydride intermediate in conjunction with a ligand assistance.[10b,31] Despite intensive investigation on complex **C** (Figure 1), the reaction mechanism remains unclear and is suggested to involve an unusual ligand participation.[28] Nevertheless, a recent report suggests the occurrence of a vacant site on the metal center.[32] In the present case, ancillary ligand assistance appears unlikely, and we propose the involvement of a metal hydride intermediate[33] in the context of an inner sphere mechanism mediated by a 16-electron species with a vacant site at the metal center. Ruthenium *tert*-butoxide complex **I1** would undergo an alkoxide group exchange with the alcohol substrate, yielding the chiral ruthenium complex **I2**. Hydride migration from the alkoxide ligand to the vacant site at the metal center would lead to the formation of an 18-electron ruthenium complex **I3**. Rotation of the ketone around the Ru−O bond in **I3** would allow the hydride migration from the metal center to the carbonyl to proceed in a nonstereoselective manner, yielding the racemic ruthenium complex **I4** (Scheme 2).

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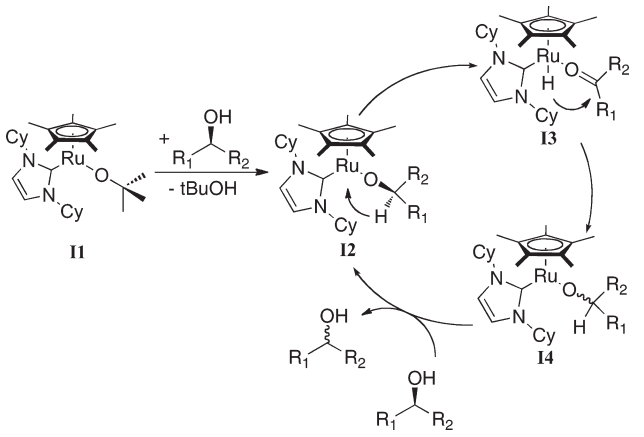
SCHEME 2. Proposed Mechanism for the Racemization of Chiral Alcohols



Conclusion

We have reported here the use of 16-electron NHC- and phosphine-containing ruthenium(II) complexes as effective catalysts in the racemization reaction of chiral alcohols and as an alternative to the currently 18-electron ruthenium(II) complexes used. One of these catalysts proved to be highly efficient in the racemization of benzylic and aliphatic alcohols at low catalyst loadings. The steric hindrance of the NHC ligand bound to ruthenium appears to be the principal factor influencing reaction rate, and the smallest NHC within the series investigated (ICy) was found to be the best enabler for this transformation. The proposed mechanism and these early catalytic racemization results pave the way for a detailed study of the factors governing this apparently "straightforward" racemization process.

Experimental Section

General Procedure for Alcohol Racemization. In a glovebox, a 4 mL vial capped with a septum is charged with [Cp*Ru(ICy)Cl] (10 mg, 0.02 mmol), NaO-*t*-Bu (2 mg, 0.02 mmol), and toluene (2 mL). Outside of the glovebox, after 10 min of stirring, the chiral alcohol (1.00 mmol) was added by syringe to the reaction mixture. This was then stirred for 30 min at rt. After this time, the reaction mixture was filtered through silica gel and evaporated to dryness. The crude material was purified by flash chromatography on silica gel (pentane/ethylacetate 9:1).

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Supporting Information Available: Procedures for the preparation of **I** and for the racemization reaction, details of the determination of $\%V_{Bur}$, HPLC traces of all compounds employed and formed, and copies of NMR spectra of compounds **1**−**6**. This material is available free of charge via the Internet at http://pubs.acs.org