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Ruthenium Hydroxide Complexes in the Racemization of Secondary Alcohols

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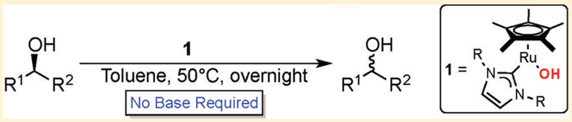
Supporting Information

ABSTRACT: Two well-defined 16-electron ruthenium hydroxide complexes were prepared and successfully used in the racemization of aromatic and aliphatic secondary alcohols. The intrinsic basicity of these new complexes permits for the exclusion of KO^{t}Bu in the racemization reaction.



Controlled racemization is of essential importance in the industrial synthesis of optically pure compounds.[1] As an application, dynamic kinetic resolution (DKR) has proven to be a powerful process in which an enantiomerically pure compound is obtained using a racemic mixture, in the presence of an enzyme reacting with only one enantiomer and a catalyst which racemizes the remaining unreacted isomer.[2] This concept has first been applied to the acetylation of alcohols by Williams[3] and then developed by Bäckvall with the use of a ruthenium-based catalyst for the racemization of alcohols and Candida Antarctica Lipase B (CAL-B) as an acylating enzyme.[4] Several catalysts have been developed for the racemization reaction,[3,5] and to date, the most active are Ru-based complexes. The prototypical example is the dinuclear catalyst **A**, shown in Figure 1, which was developed by Shvo.[6]

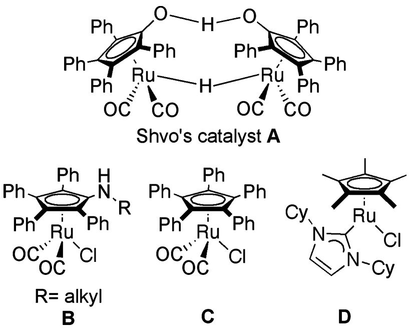
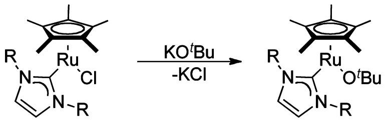


Figure 1. Ruthenium-based alcohol racemization catalysts.

Upon thermal activation, **A** dissociates to generate an 18-electron ruthenium(II) complex and the active 16-electron ruthenium(0) complex. Avoiding the required dissociation of a dimeric species, new families of 18-electron complexes were developed by Park in the form of complex **B**[7] and by Bäckvall with complex **C**.[8] These new catalysts proved their efficiency in alcohol racemization under mild conditions after *in situ* activation with sodium or potassium *tert*-butoxide. In a recent contribution, we have reported the use of well-defined 16-electron N-heterocyclic carbene (NHC) and phosphine-containing complexes enabling this transformation. Among them, complex **D** was successfully employed in the racemization of secondary alcohols, providing good catalytic racemization in only 30 min at room temperature.[9,10]

According to the accepted mechanism of the catalytic cycle involving complexes **B**−**D**, an initial reaction between the ruthenium precatalyst and KO^{t}Bu results in a metathesis reaction generating the catalytically active ruthenium alkoxide species (eq 1).[9] In the case of complexes **B** and **C**, Bäckvall



(1)

proposed this exchange to be assisted by coordinated CO.[11] In the case of complexes of type **C**, once generation of the Ru alkoxide species has occurred, CO dissociation has been proposed to be a crucial step in the formation of an active 16-electron species.[12]

We recently examined the role of *built-in* Brønsted−Lowry basic groups in gold catalysis. In this approach, a catalyst bearing a hydroxide moiety proved quite active in numerous gold-mediated transformations.[13] We reasoned that such a built-in feature[14] could also prove attractive in ruthenium-mediated racemization protocols, as it would alleviate the need for external bases and might also shed further light on the exact mechanism at play in the racemization of secondary alcohols.

The synthetic strategy led to the isolation of two novel 16-electron complexes, with the formulation [Cp*Ru(NHC)OH] (Cp* = pentamethylcyclopentadiene), that could be simply prepared from the corresponding [Cp*Ru(NHC)Cl], where NHC = IPr (1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) (**1**), IMes (1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene) (**2**). These complexes can be prepared simply by stirring [Cp*Ru(NHC)Cl] with dried CsOH overnight or in a one-pot synthesis involving the precursor [Cp*RuCl]$_4$ in the presence

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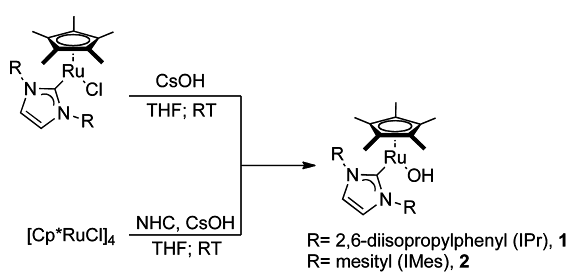
of the free NHC and CsOH.[15] Scheme 1 represents the two synthetic pathways employed.

Scheme 1. Synthesis of Complexes 1 and 2



In both cases, crystals were grown from saturated pentane solutions and single-crystal X-ray diffraction studies were performed to unambiguously confirm the molecular structures of **1** and **2** (Figure 2).[16]

Selected bond lengths and angles for **1** and **2** can be compared with data from the corresponding [Cp*Ru(NHC)-Cl] congeners.[17,18] In both cases, substituting Cl by OH does not lead to significant modification in bond lengths and angles between the NHC, Cp*, and the metal center. We can notice a reduced bond length between the ruthenium center and the hydroxide group in comparison to the analogous Ru−Cl bond (Ru−OH (Å): **1**, 2.001; **2**, 2.027).

To test the catalytic efficacy of these two new complexes, **1** and **2** were launched in the racemization reaction of (*S*)-1-phenylethanol and showed a low reactivity at room temperature with only traces of (*R*)-1-phenylethanol after 1 h. This observation could be explained by a higher stability of [Cp*Ru(NHC)OH] as compared to the *in situ* generated [Cp*Ru(NHC)(O*t*Bu)], which reacted immediately with the alcohol at room temperature. It has previously been determined that the NHC's in **1** or **2** are not the optimum ancillary ligands. ICy (ICy = 1,3-dicyclohexylimidazol-2-ylidene) has proven superior to IPr and IMes but the congener hydroxide has proven difficult to isolate to date.[9] Nevertheless, having stable hydroxides in hand, we decided to profile the racemization of (*S*)-1-phenylethanol with **1** and **2** under slightly harsher conditions (50 °C), and the results are presented in Figure 3.

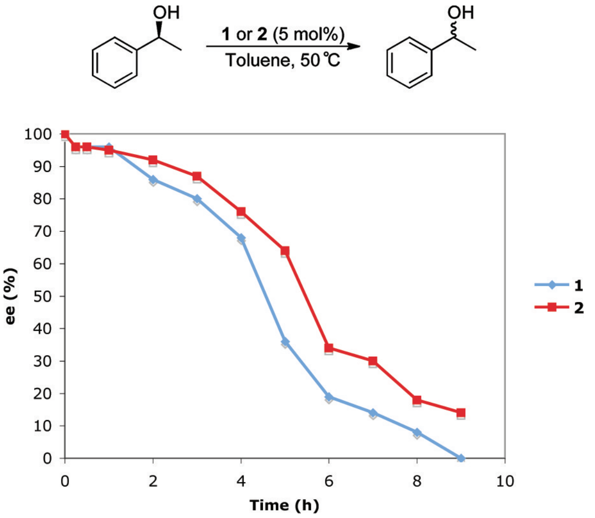


Figure 3. (*S*)-1-Phenylethanol racemization with **1** and **2**.

With both catalysts, the racemization kinetics appeared very slow in the first 1 h, characterizing an initiating period and justified by the higher stability of these well-defined complexes, and then the observed enantiomeric excess decreased rapidly to ca. 20% and a few more hours were required to observe a complete racemization in 9 h with **1** and 13 h with **2**. As the catalytic performance of **1** proved superior to that of **2**, further catalytic work was conducted with **1**.

In a previous study, the mechanism of racemization with 16-electron complexes of type **D** was investigated, leading to the formation of a Ru−H intermediate.[10] To support the formation of a similar intermediate with the new Ru−OH complexes, a stoichiometric ^{1}H NMR experiment was conducted with **1** and phenylethanol and showed a signal at −9.6 ppm, supporting the formation of a ruthenium hydride species.

A short reaction scope was examined and a number of secondary alcohols were reacted overnight at 50 °C with 5 mol % of catalyst **1**. (*S*)-1-Phenylethanol (entry 1; Table 1) was fully racemized under these conditions, as were (*S*)-2-naphtylethanol and (*R*)-*p*-chlorophenylethanol. With these three examples excellent isolated yields were obtained after simple purification (entries 2 and 3; Table 1). Unsurprisingly, an aliphatic alcohol, (*S*)-3-octanol, was also efficiently racemized and characterized after its conversion into the corresponding benzyl ester (entry 4; Table 1). With catalyst **D**, subtrates *S*-**7** and *S*-**8** proved to be less reactive toward

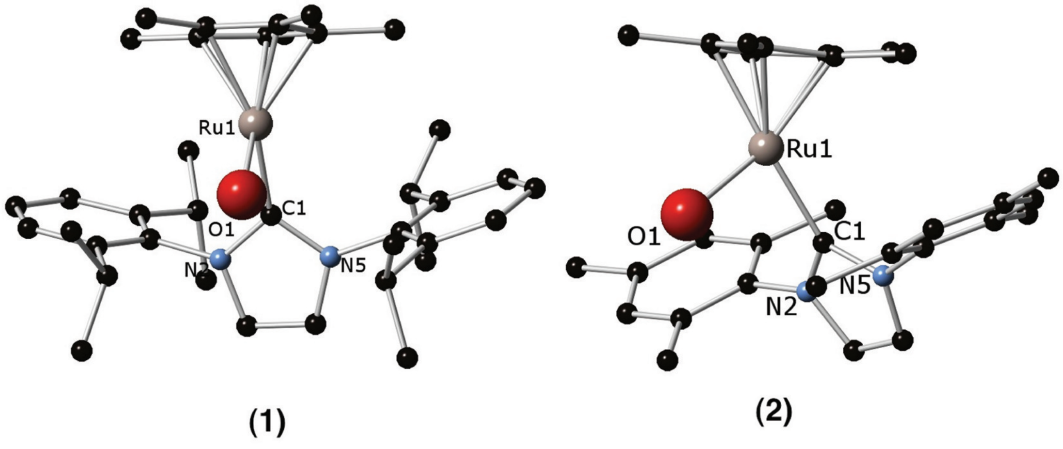
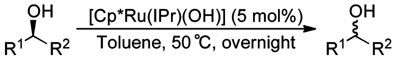
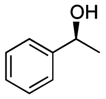
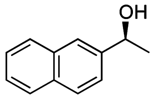
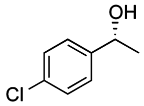
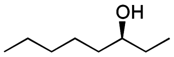
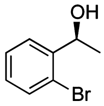
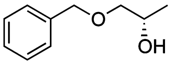


Figure 2. Molecular structures of **1** and **2**. H atoms have been omitted for clarity. Ru−OH (Å): **1**, 2.001; **2**, 2.027.

Table 1. Scope of the Racemization Reaction[a]



Entry	Substrate	Racemization (%)[b]	Yield (%)[c]
1	 S-3	>99	92
2	 S-4	>99	87
3	 R-5	>99	90
4	 S-6	>99[d]	82
5	 S-7	5	–[e]
6	 S-8	11	–[e]

[a]Typical reaction conditions: 1 mmol of alcohol, 0.05 mmol of **1**, 2 mL of toluene, overnight stirring at 50 °C. [b]Determined by HPLC analysis with Chiralcel OD-H. [c]Isolated yield after purification by column chromatography. [d]Determined after conversion into the corresponding benzyl ester. [e]Yield not measured.

racemization. Under our conditions, only small amounts of the new enantiomer could be detected, with only 5 and 11% racemization respectively detected (entries 5 and 6; Table 1). In both cases, the steric hindrance and the electron-poor nature of the substrates appear to be significant barriers for an efficient reaction with the ruthenium hydroxide.

In conclusion, we have synthesized and fully characterized, for the first time, two well-defined ruthenium hydroxide complexes from the readily available $[Cp^*RuCl]_4$ or from the corresponding [Cp*Ru(NHC)Cl]. These complexes proved to be active in the racemization of several aliphatic and aromatic alcohols. Although their catalytic activity was found wanting in comparison to the previously reported [Cp*Ru(NHC)Cl]/KO^{t}Bu catalytic systems,[9,10] the ability to perform racemization under base-free conditions may prove useful in future circumstances.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Text, tables, figures, and CIF files giving synthesis, characterization, and crystallographic data of **1** and **2** as well as the typical racemization procedure and NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) Ebbers, E. J.; Ariaans, G. J. A.; Houbiers, J. P. M; Bruggink, A.; Zwanenburg, B. *Tetrahedron* **1997**, *53*, 9417.

(2) For selected reviews on DKR: (a) Ahn, Y.; Ko, S.-B.; Kim, M.-J.; Park, J. *Coord. Chem. Rev.* **2008**, *252*, 647. (b) Conley, B. L.; Pennington-Boggio, M. K.; Boz, E.; Williams, T. J. *Chem. Rev.* **2010**, *110*, 2294. (c) Lee, J. H.; Han, K.; Kim, M.-J.; Park, J. *Eur. J. Org. Chem.* **2010**, 999. (d) Martin-Matute, B.; Bäckvall, J.-E. *Curr. Opin. Chem. Biol.* **2007**, *11*, 226. (e) Turner, N. J. *Curr. Opin. Chem. Biol.* **2010**, *14*, 115. (f) Huerta, F. F.; Minidis, A. B. E.; Bäckvall, J.-E. *Chem. Soc. Rev.* **2001**, *30*, 321. (g) Pamies, O.; Bäckvall, J.-E. *Chem. Rev.* **2003**, *103*, 3247. (h) Pellissier, H. *Tetrahedron* **2008**, *64*, 1563.

(3) Dinh, P. M.; Howarth, J. A.; Hudnott, A. R.; Williams, J. M. J.; Harris, W. *Tetrahedron Lett.* **1996**, *37*, 7623.

(4) (a) Larsson, A. L. E.; Persson, B. A.; Bäckvall, J.-E. *Angew. Chem., Int. Ed.* **1997**, *36*, 1211. (b) Persson, B. A.; Larsson, A. L. E.; Le Ray, M.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1999**, *121*, 1645.

(5) For studies on racemization reactions: (a) Berkessel, A.; Sebastian-Ibarz, M. L.; Mueller, T. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 6567. (b) Jerphagnon, T.; Gayet, A. J. A.; Berthiol, F.; Ritleng, V.; Mrsic, N.; Meetsma, A.; Pfeffer, M.; Minnaard, A. J.; Feringa, B. L.; de Vries, J. G. *Chem. Eur. J.* **2009**, *15*, 12780. (c) Marr, A. C.; Pollock, C. L.; Saunders, G. C. *Organometallics* **2007**, *26*, 3283. (d) Schnell, B.; Faber, K.; Kroutil, W. *Adv. Synth. Catal.* **2003**, *345*, 653. (e) Wuyts, S.; Wahlen, J.; Jacobs, P. A.; De Vos, D. E. *Green Chem.* **2007**, *9*, 1104. (f) J. Blacker, A.; Stirling, M. J.; Page, M. I. *Org. Process Res. Dev.* **2007**, *11*, 642. (g) Corberan, R.; Peris, E. *Organometallics* **2008**, *27*, 1954. (h) Stirling, M.; Blacker, J.; Page, M. I. *Tetrahedron Lett.* **2007**, *48*, 1247.

(6) (a) Shvo, Y.; Czarkie, D.; Rahamim, Y.; Chodosh, D. F. *J. Am. Chem. Soc.* **1986**, *108*, 7400. (b) Karvembu, R.; Prabhakaran, R.; Natarajan, K. *Coord. Chem. Rev.* **2005**, *249*, 911.

(7) (a) Choi, J. H.; Choi, Y. K.; Kim, Y. H.; Park, E. S.; Kim, E. J.; Kim, M.-J.; Park, J. *J. Org. Chem.* **2004**, *69*, 1972. (b) Choi, J. H.; Kim, Y. H.; Nam, S. H.; Shin, S. T.; Kim, M.-J.; Park, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2373.

(8) (a) Csjernyik, G.; Bogar, K.; Bäckvall, J.-E. *Tetrahedron Lett.* **2004**, *45*, 6799. (b) Martin-Matute, B.; Edin, M.; Bogar, K.; Bäckvall, J.-E. *Angew. Chem., Int. Ed.* **2004**, *43*, 6535.

(9) Bosson, J.; Nolan, S. P. *J. Org. Chem.* **2010**, *75*, 2039.

(10) Bosson, J.; Poater, A.; Cavallo, L.; Nolan, S. P. *J. Am. Chem. Soc.* **2010**, *132*, 13146.

(11) (a) Aberg, J. B.; Nyhlen, J.; Martin-Matute, B.; Privalov, T.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2009**, *131*, 9500. (b) Martin-Matute, B.; Aberg, J. B.; Edin, M.; Bäckvall, J.-E. *Chem. Eur. J.* **2007**, *13*, 6063.

(12) Warner, M. C.; Verho, O.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2011**, *133*, 2820. (b) Nyhle'n, J.; Bäckvall, J.-E *Chem. Eur. J.* **2009**, *15*, 5220.

(13) (a) Gaillard, S.; Bosson, J.; Ramon, R. S.; Nun, P.; Slawin, A. M. Z.; Nolan, S. P. *Chem. Eur. J.* **2010**, *16*, 13729. (b) Gaillard, S.; Slawin, A. M. Z.; Nolan, S. P. *Chem. Commun.* **2010**, *46*, 2742.

(14) For examples of other metal hydroxides and alkoxides see: Fulton, J. R.; Holland, A. W.; Fox, D. J.; Bergman, R. G. *Acc. Chem. Res.* **2002**, *35*, 44–56.

(15) Unfortunately, up to now, we have been unable to isolate the [Cp*Ru(ICy)OH] complex, which should prove even more active than **1** or **2**.

(16) CCDC-833140 (**1**) and CCDC-833139 (**2**) contain the supplementary crystallographic data for this contribution. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(17) Jafarpour, L.; Stevens, E. D.; Nolan, S. P. *J. Organomet. Chem.* **2000**, *606*, 49.

(18) Huang, J.; Schanz, H.-J.; Stevens, E. D.; Nolan, S. P. *Organometallics* **1999**, *18*, 2370.