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Mechanism of Racemization of Chiral Alcohols Mediated by 16-Electron Ruthenium Complexes

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Abstract: Experimental and computational analyses provide support for the existence of a metal-hydride-based mechanism for the ruthenium-mediated racemization of chiral alcohols.

Racemization protocols are often involved in industrial syntheses leading to enantiomerically pure compounds. In this context, the development of new catalysts enabling the racemization of substrates under mild conditions is of significant importance.[1] Such a simple and atom-efficient protocol is best exemplified by a dynamic kinetic resolution (DKR) process where a racemization catalyst is introduced into a kinetic resolution reaction, allowing complete conversion of a racemic alcohol into an enantiomerically pure compound.[2] An alcohol racemization can be viewed as a hydrogen transfer reaction in which a chiral alcohol is formally dehydrogenated into the corresponding ketone intermediate that subsequently undergoes a nonstereoselective transfer hydrogenation reaction.[3]

Transfer dehydrogenation of an alcohol/amine and transfer hydrogenation of a carbonyl/imine have been extensively studied.[4] Among catalysts performing alcohol racemization, ruthenium complexes exhibit remarkable activity,[5] and between these the Shvo catalyst[6,7] **A** (Figure 1) stands out and has been successfully applied in DKR.[8] Dimeric **A**, upon thermal activation, liberates two ruthenium species (**A1** and **A2**, Figure 1).[6] Casey *et al.* have reported that **A1** is the active species in carbonyl transfer hydrogenation *via* a concerted outer sphere mechanism.[9] These experimental conclusions were supported by computational studies.[10] Park and co-workers have developed a family of analogous catalysts to **A1** and applied them to the DKR of alcohol at RT (**B**, Figure 1).[11] The active species in this system is proposed to be a metal hydride that is assisted by a "participating" ligand which orients the approach of the substrate.[11b,12,13] Bäckvall and co-workers have reported a system involving a remarkably active 18-electron ruthenium catalyst (**C**, Figure 1).[14,15] Racemization using this system occurs by an inner sphere mechanism, and the formation of a keto hydride ruthenium intermediate is suggested.[16] The racemization is proposed to involve a ruthenium species possessing a vacant site, but dissociation of one of the CO ligands in **C** is not observed, even if its participation is not excluded.[17] Nevertheless, a recent report suggests the existence of a vacant site on the metal center, as **C** allows coordination of an olefin during the racemization reaction.[18] Another pathway allowing the creation of a vacant site would be an $\eta^5 \rightarrow \eta^3$ Cp ring slippage, but the high energy required for this process is not in line with the mild operational conditions of the reaction.[19] On the other hand, the energy profile calculated for a pathway involving a CO ligand dissociation suggests this route may lead to a vacant site.[19] Despite its impressive activity toward alcohol racemization, the route providing the vacant site on the metal center allowing the formation of a keto hydride ruthenium intermediate, as presumably involved with the Bäckvall-type catalyst, remains uncertain. We recently reported that 16-electron ruthenium complexes bearing *N*-heterocyclic carbene (NHC)[20] ligands (**D**,[21] Figure 1) are efficient catalysts for the racemization of aromatic and aliphatic alcohols, able to achieve this transformation at RT with low catalyst loadings and within minutes.[22] This system is a rare example of a well-defined 16-electron ruthenium catalyst in racemization reactions[23] and is analogous to **A2**. This well-defined species bearing an NHC ligand known to ease intermediate stabilization[20] affords a unique opportunity to address fundamental mechanistic questions related to ruthenium-based racemization catalysis.

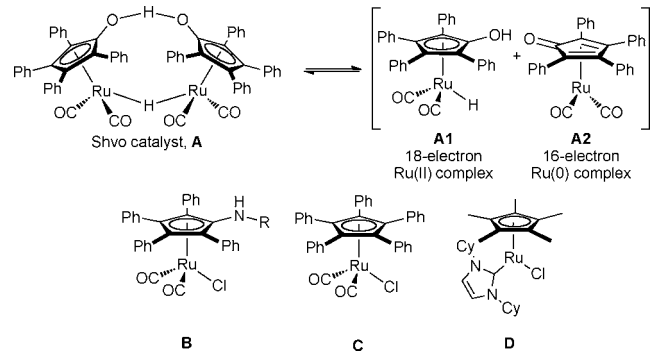

Figure 1. Ruthenium catalysts for the racemization of chiral alcohols, R = alkyl, Cy = C_6H_{11}.

The racemization of chiral alcohols mediated by **D** was proposed to proceed by an inner-sphere pathway, and treatment of **D** with NaO^{t}Bu leads to the formation of the corresponding Ru−O^{t}Bu (**E**). This species would undergo ligand exchange with the alcohol substrate, leading to the formation of **F** and entry into the catalytic cycle (Scheme 1). β-Hydride transfer from the alkoxide ligand in **F** to the metal vacant site and concomitant coordination of the resulting ketone would afford an 18-electron hydride complex **I**. The involvement of a Ru−H species has previously been suggested.[16,22,24] Rotation of the σ-coordinated ketone around the Ru−O bond in **I** associated with the nonstereospecific return of the H atom onto the ketone would allow the formation of the racemic ruthenium complex **F′**.

In order to support the hypothesis that the present racemization proceeds through a hydride ruthenium complex, the racemization

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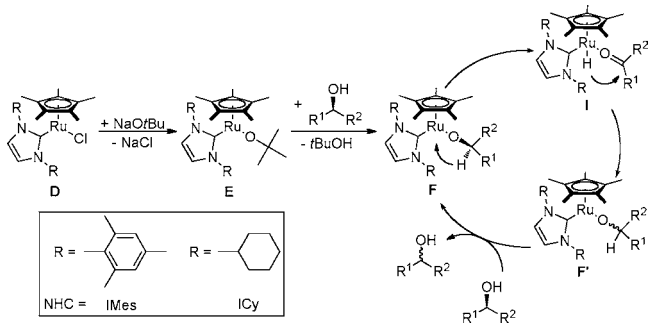
Scheme 1. Proposed Mechanism for Racemization of Chiral Alcohols Mediated by 16-Electron Ruthenium Complexes



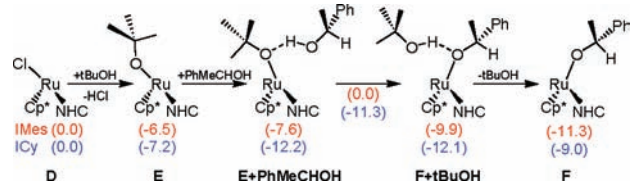
of *S*-phenylethanol by the [Cp*Ru(ICy)Cl]/NaO*t*Bu system was monitored by NMR spectroscopy.

A ^{1}H NMR experiment in toluene-d_8 revealed the formation of three hydride ruthenium complexes of unequal intensities during the racemization process, with chemical shifts at −9.64, −9.67, and −9.70 ppm, respectively (see Supporting Information (SI)). Decreasing the NMR analysis temperature from 293 to 253 K did not affect these results. A ^{13}C NMR experiment exhibited three resonances in the 190 ppm range, at 197.34, 196.45, and 194.45 ppm (see SI). None belong to free acetophenone, which exhibits a carbonyl carbon chemical shift at 195.92 ppm. HMBC experiments indicated a correlation between the carbon atom at 197.34 ppm with a hydrogen atom at 6.60 ppm—hydrogen atom from the NHC backbone—indicating that this carbon atom is a carbenic carbon from the NHC. The carbon at 196.45 ppm correlated with hydrogens at 2.23 ppm, suggesting that this carbon is associated with a carbonyl group. Moreover, the acetophenone methyl group exhibits a ^{1}H NMR resonance at 2.08 ppm in toluene-d_8, so this carbon atom is not associated with free acetophenone. Concerning the carbon atom at 194.45 ppm, correlations with two different hydrogen groups in the 2.50−2.20 ppm range were observed, but no specific assignment could unambiguously be made. Carrying out these experiments with labeled 1-^{13}C-phenylethanol confirmed that the carbon atom at 196.45 ppm is a compound obtained from the starting alcohol, supporting an inner-sphere mechanism, as previously proposed.[22] However, no correlation between the hydrides and the carbonyl carbon atom could be observed, even when employing a labeled starting alcohol.

To further support the proposed mechanism for phenylethanol racemization mediated by 16-electron ruthenium complexes, a computational analysis of the reaction pathway was undertaken and two NHC ligands were examined,[25] namely ICy (1,3-dicyclohexylimidazol-2-ylidene) and IMes (1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene) (Scheme 1).[26] We have previously reported a dramatic ligand influence on the racemization reaction associated with NHC ligand sterics. The ICy ligand proved to be highly efficient, while its more sterically demanding IMes counterpart permitted only moderated conversions.[22]

As described above, catalysis initiation involves the transformation of **D** into **E** and occurs by treatment of **D** with sodium *tert*-butoxide. This step is thermodynamically favored by 6.5 and 7.2 kcal·mol^{-1} for ICy and IMes, respectively (Scheme 2). Exchange from the *tert*-butoxide ligand to phenylethanolate (complex **F**) revealed to be slightly favored in both cases, but only by 1.8 kcal·mol^{-1} in the case of ICy, whereas for IMes complex **F** is favored by 4.8 kcal·mol^{-1}, probably due to the more important steric hindrance of the *tert*-butoxide ligand compared to phenylethanolate. The H-transfer step from the H-bonded phenylethanol to the *tert*-butoxide ligand in **E** costs 7.6 kcal·mol^{-1} in the case of IMes, whereas for ICy the barrier is negligible, only 0.9 kcal·mol^{-1}.[27] Finally, it is noteworthy that entropic effects, not included in the present calculations, would disfavor phenylethanol H-bonding to **E**, thus increasing the barrier for activation.

Scheme 2. Thermodynamics of the Initiation Step, in kcal·mol^{-1}



Complex **F** is the entrypoint into the racemization catalytic cycle (see Figure 2) and is set as the zero energy point for the following discussion. The C_β−H bond of **F** engages in a β-agostic interaction with the Ru center in **G**. Differences between the ICy and IMes systems are already striking, with the β-agostic IMes complex **G** lying 17.5 kcal·mol^{-1} above **F**, whereas the ICy complex **G** is only 5.1 kcal·mol^{-1} above **F**. β-H elimination from **G** leads to the π-coordinated ketone Ru-hydride complex **H**. Again, the IMes complex is roughly 10 kcal·mol^{-1} higher in energy relative to the ICy complex.[28] The fact that the two transition states surrounding the β-agostic complex **G** are less than 5 kcal·mol^{-1} higher in energy is evidence that **G** is a rather unstable intermediate. The π-coordinated ketone Ru−hydride complex **H** can evolve with barriers of approximately 15 and 18 kcal·mol^{-1} to the σ-coordinated ketone Ru−hydride complex **I**, which are roughly 5 kcal·mol^{-1} less stable than the π-coordinated ketone Ru-hydride complex **H**. Complex **I** is essentially at the midpoint along the racemization reaction pathway.

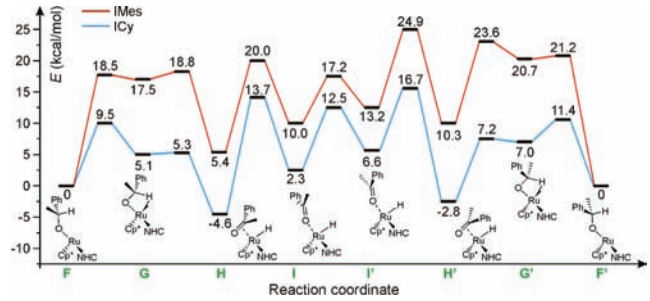


Figure 2. Schematic reaction pathway for the transformation of *R*-phenylethanol into *S*-phenylethanol promoted by [Ru(NHC)(Cp*)Cl]. Red, NHC = IMes; Blue, NHC = ICy.

In fact, rotation around the Ru−O σ-bond of the σ-coordinated ketone, with a barrier spanning 7 to 10 kcal·mol^{-1}, leads to another σ-coordinated ketone, **I′** in Figure 2, with a different orientation of the Ph and Me groups relative to the NHC and Cp* ligands. The σ-coordinated ketone **I′** collapses into the π-coordinated ketone **H′**, which corresponds to a change in the enantioface of the ketone coordinated to the metal. Insertion of the C═O of **H′** into the Ru−hydride bond leads to the β-agostic intermediate **G′**, that rapidly loses the agostic interaction leading to the final complex **F′**. Overall, the pathway from **F** to **F′** corresponds to an inversion of configuration at the C_β atom of the alkoxide. The overall energy barrier, estimated as the energy difference between the **I′** to **H′** transition state and intermediate **H**, amounts to 21.3 kcal mol^{-1} for ICy.

All along the reaction pathway, the intermediates and transition states associated with the IMes complex are roughly 10 kcal·mol^{-1} higher in energy than those for the ICy complex. This is due to the increased steric bulk of IMes relative to ICy and is evidenced by the

IMes−Ru−Cp* angle, which is 4.2° larger than the ICy−Ru−Cp* angle, on average, along the reaction pathway. Further support for this hypothesis emerges from the analysis of the key β-agostic intermediate **G** (Figure 3). In addition to the larger NHC−Ru−Cp* angle, the higher steric stress of the system bearing the IMes ligand is evidenced by the shorter Ru−O distance and by the quite longer Ru−H agostic distance. Indeed, in the case of ICy the C_β−H distance is remarkably long, and the overall complex resembles the π-coordinated ketone species **H**. The major source of steric stress in the case of the IMes complex involves the interaction between the Me group on the C_β atom, which is a short distance from one of the Me_{ortho} groups of the nearby mesityl ring, and forces a remarkable rotation of this ring around the $N-C_{ipso}$ bond (the $C_{carbene}-N-C_{ipso}-C_{ortho}$ dihedral angle is 115.5°). This rotation is limited by steric interaction between the other Me_{ortho} group and Me groups of the Cp* ligand. The increased steric stress in these NHC complexes can be quantified by the total percent buried volume, $\%V_{Bur}$,[26,29] occupied by the NHC and the Cp* ligands in the IMes complex (73.6%) vs the smaller value of 70.3% for the ICy complex.[29a]

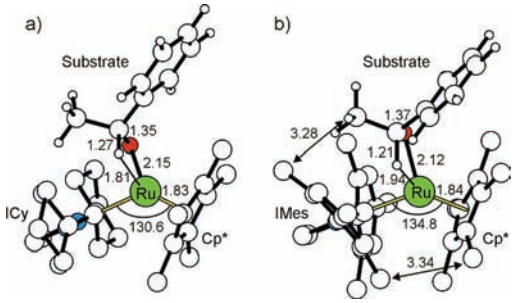


Figure 3. DFT structure of the β-agostic intermediates. Distances in Å, angles in deg. (a and b) NHC = ICy and IMes, respectively.

The reaction moves to completion by release/exchange of the racemized phenylethanolate ligand with a free alcohol molecule, through proton transfer (Figure 4). This step begins with the approach of a free alcohol molecule to the coordinated alkoxide **F′** via a H-bond interaction, as in intermediate **J′**, which is 0.9 above and 1.9 kcal·mol^{-1} below **F′** for IMes and ICy, respectively. This indicates a clear steric stress in the H-bonded intermediate **J′**. The proton transfer reaction proceeds through transition state **J′**−**J** with a barrier of 10.3 kcal·mol^{-1} for IMes, while it is remarkably lower for ICy, only 1.8 kcal·mol^{-1}. The system collapses into the H-bonded complex **J**, from which the racemized alcohol is released. Finally, it is noteworthy that entropic effects, not included in the present calculations, would disfavor phenylethanol H-bonding to **F′**, thus increasing the barrier for alcohol exchange.

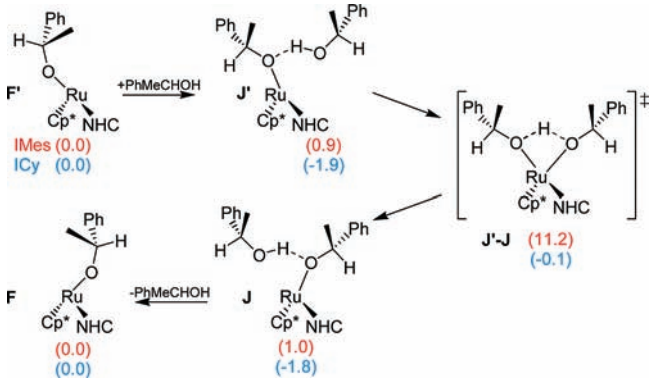


Figure 4. Schematic reaction pathway for release of the racemized alcohol, energies in kcal·mol^{-1}.

Comparison of the overall racemization pathway indicates that, in the case of ICy, the magnitude of all energy barriers supports a ruthenium-mediated racemization reaction occurring at room temperature. Conversely, in the case of IMes, several intermediates and transition states are significantly higher in energy, an energy profile which is in qualitative agreement with the reduced racemization activity of the Ru−IMes complex.

In the context of the development of new catalysts enabling alcohol racemization, we previously reported the use of highly efficient 16-electron ruthenium complexes. Here, we support a proposed reaction mechanism by spectroscopic detection of intermediates that are analyzed by computational methods. These results clearly highlight a mechanism involving ruthenium hydride intermediates, without any direct ligand participation. Furthermore, the reaction mechanism proposed consists of a sequence of reaction steps among the most typical in organometallic chemistry: β-H elimination, π to σ isomerization of a coordinated ketone, and ketone insertion into the Ru−H bond.

We believe these results will prove helpful in the understanding of the mechanism of other racemization catalysts and should guide the development of new catalysts for racemization reactions.

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Supporting Information Available: NMR data supporting the existence of hydride intermediates and full computational material. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Ebbers, E. J.; Ariaans, G. J. A.; Houbiers, J. P. M.; Bruggink, A.; Zwanenburg, B. *Tetrahedron* **1997**, *53*, 9417–9476.
(2) (a) Huerta, F. F.; Minidis, A. B. E.; Bäckvall, J.-E. *Chem. Soc. Rev.* **2001**, *30*, 321–331. (b) Pamies, O.; Bäckvall, J.-E. *Chem. Rev.* **2003**, *103*, 3247–3261. (c) Pellissier, H. *Tetrahedron* **2008**, *64*, 1563–1601.
(3) *Hydrogen-Transfer Reactions*; Wiley-VCH: Weinheim, 2007.
(4) For reviews on H transfer reactions, see: (a) Samec, J. S. M.; Bäckvall, J.-E.; Andersson, P. G.; Brandt, P. *Chem. Soc. Rev.* **2006**, *35*, 237–248. (b) Normand, A. T.; Cavell, K. J. *Eur. J. Inorg. Chem.* **2008**, 2781–2800. (c) Gladiali, S.; Alberico, E. *Chem. Soc. Rev.* **2006**, *35*, 226–236. (d) Saluzzo, C.; Lemaire, M. *Adv. Synth. Catal.* **2002**, *344*, 915–928.
(5) Mavrynsky, D.; Sillanpaa, R.; Leino, R. *Organometallics* **2009**, *28*, 598–605.
(6) Shvo, Y.; Czarkie, D.; Rahamim, Y.; Chodosh, D. F. *J. Am. Chem. Soc.* **1986**, *108*, 7400–7402.
(7) For reviews on the Shvo catalyst, see: (a) Prabhakaran, R. *Synlett* **2004**, 2048–2049. (b) Karvembu, R.; Prabhakaran, R.; Natarajan, K. *Coord. Chem. Rev.* **2005**, *249*, 911–918. (c) Conley, B. L.; Pennington-Boggio, M. K.; Boz, E.; Williams, T. J. *Chem. Rev.* **2010**, *110*, 2294–2312.
(8) Larsson, A. L. E.; Persson, B. A.; Bäckvall, J.-E. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1211–1212.
(9) Casey, C. P.; Singer, S. W.; Powell, D. R.; Hayashi, R. K.; Kavana, M. *J. Am. Chem. Soc.* **2001**, *123*, 1090–1100.
(10) (a) Comas-Vives, A.; Ujaque, G.; Lledós, A. *Organometallics* **2007**, *26*, 4135–4144. (b) Comas-Vives, A.; Ujaque, G.; Lledós, A. *J. Mol. Struc. (Theochem)* **2009**, *903*, 123–132.
(11) (a) Choi, J. H.; Kim, Y. H.; Nam, S. H.; Shin, S. T.; Kim, M.-J.; Park, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2373–2376. (b) 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*, 1972–1977.
(12) Casey, C. P.; Johnson, J. B.; Singer, S. W.; Cui, Q. *J. Am. Chem. Soc.* **2005**, *127*, 3100–3109.
(13) For a review on bifunctionnal catalysts, see: Ikariya, T.; Blacker, A. J. *Acc. Chem. Res.* **2007**, *40*, 1300–1308.
(14) Martin-Matute, B.; Edin, M.; Bogar, K.; Bäckvall, J.-E. *Angew. Chem., Int. Ed.* **2004**, *43*, 6535–6539.
(15) Csjernyik, G.; Bogar, K.; Bäckvall, J.-E. *Tetrahedron Lett.* **2004**, *45*, 6799–6802.
(16) Martin-Matute, B.; Edin, M.; Bogar, K.; Kaynak, F. B.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2005**, *127*, 8817–8825.
(17) (a) Martin-Matute, B.; Aberg, J. B.; Edin, M.; Bäckvall, J.-E. *Chem.—Eur. J.* **2007**, *13*, 6063–6072. (b) Aberg, J. B.; Nyhlen, J.; Martin-Matute, B.; Privalov, T.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2009**, *131*, 9500–9501.

(18) Aberg, J. B.; Warner, M. C.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2009**, *131*, 13622–13624.
(19) Nyhlen, J.; Privalov, T.; Bäckvall, J.-E. *Chem.—Eur. J.* **2009**, *15*, 5220–5229.
(20) For a review on NHC ligands in LTM catalysis, see: Díez-González, S.; Marion, N.; Nolan, S. P. *Chem. Rev.* **2009**, *109*, 3612–3676.
(21) (a) Huang, J.; Schanz, H.-J.; Stevens, E. D.; Nolan, S. P. *Organometallics* **1999**, *18*, 2370–2375. (b) Jafarpour, L.; Stevens, E. D.; Nolan, S. P. *J. Organomet. Chem.* **2000**, *606*, 49–54.
(22) Bosson, J.; Nolan, S. P. *J. Org. Chem.* **2010**, *75*, 2039–2043.
(23) For a patent on Noyori-type catalysts in a DKR reaction, see: Verzijl, G. K.; De Vries, J. G.; Broxterman, Q. B. WO/2001/090396, 2001. The activity of a putative 16-electron ruthenium species has been reported in alcohol racemization: (c) Ito, M.; Osaku, A.; Kitahara, S.; Hirakawa, M.; Ikariya, T. *Tetrahedron Lett.* **2003**, *44*, 7521–7523.
(24) For a review on M−H intermediates in H transfer reactions, see: Bäckvall, J.-E. *J. Organomet. Chem.* **2002**, *652*, 105–111.
(25) The BP86 DFT calculations were performed with the Gaussian03 package using an SVP basis set on main group atoms and the SDD-ECP basis set on Ru. Solvent effects, toluene, were included with the PCM approach. Free energies in solution with all nonelectrostatic effects are discussed in the text; other details are provided in the SI.
(26) (a) Jacobsen, H.; Correa, A.; Poater, A.; Costabile, C.; Cavallo, L. *Coord. Chem. Rev.* **2009**, *253*, 687–703. (b) Poater, A.; Ragone, F.; Giudice, S.; Costabile, C.; Dorta, R.; Nolan, S. P.; Cavallo, L. *Organometallics* **2008**, *27*, 2679–2681.
(27) Due to a lower energy barrier, the transition state for ICy was approximated through a linear transit scan on the *t*BuO. .H distance.
(28) Since **H** seems to be the resting state in the reaction with ICy, its stability was tested versus the **F** species with the B3LYP functional and with the last generation M06L and M06 functionals. The M06L and M06 functionals, in agreement with the BP86 functional, predict **H** to be more stable than **F** by 4.5 and 2.5 kcal·mol^{-1}, whereas the B3LYP functional predicts **F** to be more stable by 1.2 kcal·mol^{-1}.
(29) (a) Poater, A.; Cosenza, B.; Correa, A.; Giudice, S.; Ragone, F.; Scarano, V.; Cavallo, L. *Eur. J. Inorg. Chem.* **2009**, 1759–1766. (b) Poater, A.; Cavallo, L. *Dalton Trans.* **2009**, 8885–8890.

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