

Developing new vanadium complexes and new ligands for electrophilic fluorination

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Developing New Vanadium Complexes and New Ligands for Electrophilic Fluorination

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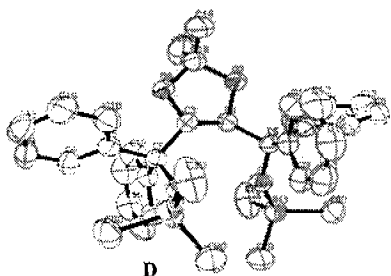
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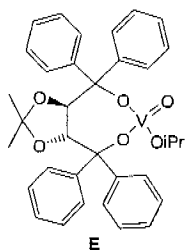
Abstract

This thesis is divided in two main parts dealing with the development of new vanadium catalysts and new ligands, respectively, for the electrophilic fluorination.

The second chapter concerns the study of vanadium complexes. Preliminary reactions using vanadium(V and IV) complexes in electrophilic fluorination of β -ketoester prompted us to prepare chiral vanadium catalysts. The search for reactions conditions for the formation of VO(TADDOLate) complexes has been carried out starting from different vanadium precursors, such as VOCl_3 , $\text{VO}(\text{O}^i\text{Pr})_3$ and $\text{VO}(\text{OSiPh}_3)_3$.



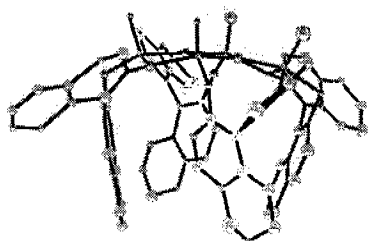
The reaction between VOCl_3 and TADDOL gave a mixture of products and none of them could be isolated. The formation of HCl as by-product can probably open the ketal group of the ligand. An approach to avoid the formation of HCl during the reaction was to synthesise a silyl-TADDOL ligand (**D**) knowing that silylethers can react with transition metal halides forming the corresponding alkoxo complexes. The synthesis of compound **D** was reported here for the first time and product **D** has been isolated and fully characterised, including a crystal structure analysis.



The reaction of TADDOL with $\text{VO}(\text{O}^i\text{Pr})_3$ gave better results than with VOCl_3 . The direct coordination of TADDOL to the vanadium(V) centre has been observed and compound **E** was fully characterised. Unfortunately, this complex was not an active catalyst for the electrophilic fluorination. The lack of reactivity was not very surprising since the vanadium precursor $\text{VO}(\text{O}^i\text{Pr})_3$ also gave no conversion of β -ketoester with an electrophilic agent.

$\text{VO}(\text{OSiPh}_3)_3$ was also used as vanadium precursor for the formation of new complexes. The good reactivity of the precursor in fluorination catalysis was very encouraging. The first reaction test using menthol as a ligand was performed in NMR tube and monitored by ^{51}V NMR spectroscopy. In the spectrum, the signal of the corresponding $[\text{VO}(\text{OSiPh}_3)_2(\text{menthoxo})]$ complex was observed along with that of $\text{VO}(\text{OSiPh}_3)_3$.

Unfortunately, it has been established that the reaction equilibrium was driven towards the $\text{VO}(\text{OSiPh}_3)_3$ upon evaporation of the solvent and no menthoxo complexes could be isolated.

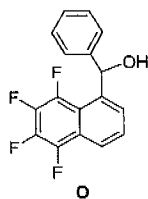


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Finally, tests in the coordination chemistry of vanadium(V) and binaphthols were performed under ^{51}V NMR spectroscopical monitoring. A common signal was found and it was tried to isolate the corresponding product. However, an interesting observation was the formation of cluster **I** instead of a monomeric complex, as expected.

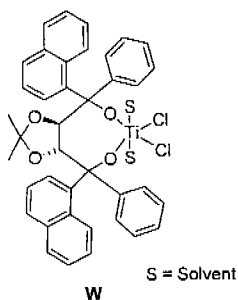
Such vanadium clusters are not so uncommon and they are especially obtained when the ligand is a bidentate one. Unfortunately, a pure monomeric vanadium complex with a bidentate ligand could not be isolated in any of the experiments.

The last part of this chapter concerned the synthesis of vanadium(IV)salen complexes. We found that the achiral V(IV)salen catalysed the fluorination reaction and encouraged the exploration of chiral vanadium(IV) complexes. The same catalysis performed with the compound **K** ($\text{VO}(\text{salen}^*)$) gave also the fluorinated β -ketoester but in a racemic form. The chiral dichlorovanadium(IV)salen complex (**2.46**) was prepared and tested, after chloride abstraction, as catalyst in fluorination reactions, however without conversion of the β -ketoester.



Chapter three presents the development of novel TADDOL derivatives for electrophilic fluorination. The modification of these ligands by replacing the naphthyl groups with a tetrafluoronaphthalenyl unit was not successful. During the synthesis of the 5,6,7,8-tetrafluoro-1-naphthol (**M**), a hydrogen bond interaction between a fluorine and the proton from the hydroxy group was studied by NMR spectroscopy ($\text{F} \cdots \text{HO}$). The ^{19}F NMR characterisation of 5,6,7,8-tetrafluoro-1-naphthol (**M**) and 1-bromo-5,6,7,8-tetrafluoronaphthalene (**N**) have not been described in the literature previously. The low reactivity of the Grignard reagent derived from compound **N**, with different electrophiles such as esters, aldehydes or ketones proves that the fluorine substituents drastically reduce nucleophilicity. Only in the case of the lithiated **N** addition to an aldehyde could be observed. The corresponding compound **O** was fully characterised.

The second modification applied to the TADDOL ligand was to form a C_2 symmetrical ligand bearing a phenyl and a naphth-1-yl group at each carbinol centre. The synthesis was achieved from corresponding aryl diketones (either phenyl or naphtha-1-yl derived from tartaric acid) upon addition of the second aryl group as a Grignard reagent. Starting from the phenyl ketone derivative only one isomer of C_1 symmetry could be isolated: (R,R,R,S) phenyl-Np-TADDOL (**T**). However, the addition of PhMgBr to the naphthyl ketone gave a mixture of three stereoisomers: one with a C_1 symmetry (R,R,R,S) and the other two with a C_2 symmetry (R,R,R,R) or (S,R,R,S). These stereoisomers were characterised by ^1H and ^{13}C NMR spectroscopy.

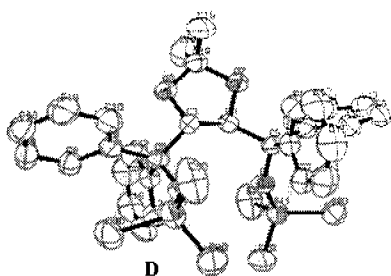


Finally, the complexation reaction of compound **T** with titanium(IV) was successful and the product was characterised by NMR analysis. Unfortunately, the test in fluorination catalysis gave only racemic product.

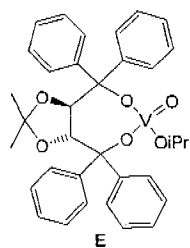
Résumé

Cette thèse est divisée en deux principaux sujets : le développement de nouveaux complexes de vanadium et de nouveaux ligands pour la fluoration électrophile.

Le second chapitre présente l'étude de complexes de vanadium. Les premiers résultats obtenus en fluoration électrophile de β -cétoesters utilisant des complexes de vanadium (IV et V), nous ont encouragés à synthétiser des catalyseurs chiraux de vanadium. La formation du complexe [VO(TADDOLate)] était l'un des objectifs de cette thèse. Plusieurs conditions expérimentales ont été testées (changement de température et de solvant) ainsi que différents précurseurs de vanadium tels que VOCl_3 , $\text{VO}(\text{O}^i\text{Pr})_3$ et $\text{VO}(\text{OSiPh}_3)_3$.



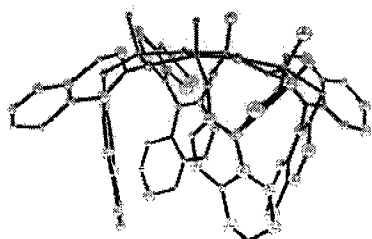
La réaction entre VOCl_3 et le ligand TADDOL aboutit à un mélange de produits dont aucun n'a peut-être isolé. Lors de cette réaction la déprotonation des deux groupes alcools du ligand ainsi que la dissociation d'un chlore du précurseur VOCl_3 entraîne la formation de HCl . Ce dernier étant vraisemblablement responsable de l'ouverture du groupement cétal du ligand. Une autre approche a été essayée afin d'éviter la présence de HCl pendant la réaction. Celle-ci consiste à synthétiser un TADDOL silylé (**D**) sachant que les silylethers peuvent réagir avec des métaux de transitions halogénés pour former les complexes correspondants. La synthèse du composé **D** est reportée ici pour la première fois. Le produit **D** a été totalement caractérisé et a fait également l'objet d'une étude structurale par diffraction des rayons X.



De meilleurs résultats ont été obtenus lors de la réaction entre le ligand TADDOL et le précurseur $\text{VO}(\text{O}^i\text{Pr})_3$. En effet, la coordination directe du ligand au vanadium(V) a été observée et le composé **E** a été totalement caractérisé. Malheureusement, **E** ne s'avère pas être un catalyseur actif en fluoration électrophile. Cette absence de réactivité n'est pas vraiment surprenante puisque $\text{VO}(\text{O}^i\text{Pr})_3$ donne également aucune conversion du β -cétoesters en présence d'un agent fluorant électrophile.

$\text{VO}(\text{OSiPh}_3)_3$ a été utilisé comme précurseur de vanadium pour la formation de complexes. Sa réactivité en catalyse de fluoration s'est avéré être très encourageante. Le premier test de

complexation utilisant le ligand menthol a été effectuée dans un tube RMN et suivi par spectroscopie RMN ^{51}V . Dans le spectre RMN deux signaux ont été observés : l'un correspondant au produit de départ $\text{VO}(\text{OSiPh}_3)_3$ et l'autre au complexe $[\text{VO}(\text{OSiPh}_3)_2(\text{menthoxo})]$. L'évaporation du solvant entraînant également celle du menthol pousse l'équilibre de réaction vers $\text{VO}(\text{OSiPh}_3)_3$ de ce fait aucun complexe n'a pu être isolé.

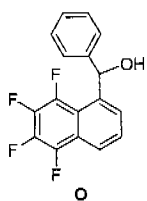


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Finally, coordination tests of binaphthol with vanadium(V) were carried out and followed by ^{51}V NMR spectroscopy. In the different spectra a common signal is observed but the isolation of the product corresponding to it was unsuccessful. Nevertheless, an interesting result was obtained: the formation of cluster **I** instead of a monomer as expected.

De similaires clusters de vanadium, formés généralement à partir de ligands bidentates, ont déjà été reportés dans la littérature. Malheureusement, lors de ces expériences aucun complexe monomérique de vanadium ayant un ligand bidentate n'a pu être isolé.

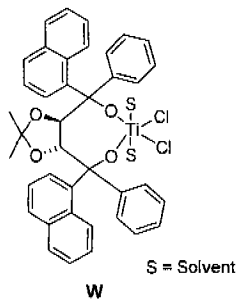
The last part of this second chapter concerns the synthesis of vanadium(IV) salen complexes. It is worth noting that the achiral complex $[\text{V}(\text{IV})\text{salen}]$ catalyzes the fluorination reaction. This result encouraged us to explore chiral vanadium(IV) complexes. The same catalysis was realized using compound **K** $[\text{VO}(\text{salen}^*)]$ to form the β -fluoro ester. The chiral complex $[\text{V}^{\text{IV}}\text{Cl}_2\text{salen}]$ (**2.46**) was prepared and tested, after abstraction of chlorides, as a catalyst for the fluorination reaction but unfortunately no conversion of the substrate was observed.



The third chapter of this thesis presents the development of new derivatives of TADDOL for electrophilic fluorination. The modification of these ligands by replacing naphthyl groups with fluorinated naphthyls was unsuccessful. However, during the synthesis of 5,6,7,8-tetrafluoro-1-naphthol (**M**), a hydrogen bond was identified by NMR spectroscopy between a fluorine atom of the naphthalene and the proton of the hydroxyl group (F---OH). The characterization of products 5,6,7,8-tetrafluoro-1-naphthol (**M**) and 1-bromo-5,6,7,8-tetrafluoronaphthalene (**N**) by ^{19}F NMR spectroscopy had never been described in the literature. The low reactivity of the Grignard derivative of compound **N** towards different

électrophiles tels qu'esters, aldéhydes ou cétones montre que les fluors réduisent nettement la nucléophilicité. Toutefois dans le cas du composé N lithié l'addition à un aldéhyde a été observée. Le composé résultant de cette réaction a pu être totalement caractérisé.

La seconde modification appliquée au ligand TADDOL fut la formation d'un ligand de symétrie C_2 portant sur chacun de ces carbinol un groupe phenyl et un groupe naphth-1-yl. La synthèse a été effectuée à partir de dicétones arylés correspondantes (phenyl ou naphth-1-yl dérivant de l'acide tartrique) en additionnant le second groupement aryl par une réaction de Grignard. Partant de la dicétone phenylé un seul isomer de symétrie C_1 a été isolé : (*R,R,R,S*) phenyl-Np-TADDOL (**T**). Cependant l'addition du PhMgBr à la dicétone naphthylé résulte en un mélange de trois stéréoisomères : un de symétrie C_1 (*R,R,R,S*) et les deux autres de symétrie C_2 (*R,R,R,R*) or (*S,R,R,S*). Ces trois stéréoisomères ont été caractérisés par spectroscopie RMN ^1H et ^{13}C .



Finalement, la complexation du ligand **T** avec le titane(IV) a été réalisée avec succès et le complexe **W** a été caractérisé par analyses RMN. Cependant le test de ce complexe en catalyse aboutit seulement au produit racémique.