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ARTICLE

Synthesis, characterization, catalytic and biological application of half-sandwich ruthenium complexes bearing hemilabile (κ2–*C*,*S*)-thioether-functionalised NHC ligands.

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A series of cationic Ru(II)(η^6-*p*-cymene) complexes with thioether-functionalised N-heterocyclic carbene ligands have been prepared and fully characterized. Steric and electronic influence of the R thioether substituent on the coordination of the sulfur atom was investigated. The molecular structure of three of them has been determined by means of X-ray diffractometry and confirmed the bidentate (κ^2-C,S) coordination mode of the ligand. Interestingly, only a single diastereomer, as an enantiomeric couple, was observed in the solid state for complexes **1c**, **1i** and **1j**. DFT calculations established a low energy inversion barrier between the two diastereomers through a sulfur pyramidal inversion pathway with R donating group while a dissociative/associative mechanism is more likely with R substituents that contain electron withdrawing group, thus suggesting that the only species observed by the ^{1}H-NMR correspond to an average resonance position of a fluxional mixtures of isomers. All these complexes were found to catalyse the oxydant-free double dehydrogenation of primary amine into nitrile. Ru complex bearing NHC-functionalised S-*t*Bu group was further investigated in a wide range of amines and was found more selective for alkyl amine substrates than for benzylamine derivatives. Finally, preliminary results of the biological effects on various human cancer cells of four selected Ru complexes are reported.

Introduction

Since the pioneering work of Murahashi[1] and Milstein[2] on acceptorless dehydrogenation (AD) type amidation, numerous groups have explored this exciting catalytic-type reaction.[3] Ruthenium has been established as the metal of choice for this highly atom-economic and environmentally friendly transformation.[4] Consequently, a wide-array of Ru-based catalyst systems have been developed for the dehydrogenation of alcohol.[3a, 3b, 3d, 5] In this context, Ru-complexes bearing N-Heterocyclic carbenes (NHCs), as synthetically accessible and highly tuneable ligand,[6] either generated in situ[7] or well-defined,[8] are particularly interesting for this process. It is noteworthy to mention that NHC-Ru catalytic system has been successfully applied with great effectiveness to amination reaction as recently disclose by Huynh *et al*.[9] Interestingly, addition of PPh_3 is frequently required with monodentate NHC-based systems to enhance the catalytic activity.[7a, 7e, 8a, 8c, 8e, 8f] N-functionalized NHCs with an additional donor group (typically P, O or N) have become an important class of bidentate ligand due to the possible hemilabile behaviour of their Lewis base moiety.[10] Few successful examples of bidentate NHC-pyrimidine,[11] -naphtylridine,[12] -picolyl,[13] -phosphine[14] and phenyl ($C^{NHC}C$)[8l, 15] Ru(arene) complexes have been reported for such acceptorless/borrowing hydrogen reactions.

Applying this AD strategy on amine is providing access to very important class of molecule namely: imine[16] and nitrile.[17, 18] In contrast with alcohols, highly selective dehydrogenations of amine mediated by transition metal are rare.[3e, 19] Reports on the double dehydrogenation of primary amines to produce nitriles and H_2 gas as the sole by-product are even scarcer.[19] Among those examples, catalysts achieve either low conversion[20] or require exogenous additives (bases and/or sacrificial hydrogen acceptor)[21] with high reaction temperature and only few avoid the use of excess oxidant or aerobic conditions.[22] Furthermore, the competition between the second dehydrogenation and the transamination pathway often lead to selectivity issues.[3e, 4] Nevertheless, this straightforward strategy represents a much delicate and greener alternative to *classic* nitrile syntheses which often

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† *Electronic Supplementary Information (ESI) available: General experimental procedures, additional schemes and figures, characterization data and NMR spectra.* crystallographic information, and atomic coordinates of the optimized species. CCDC 1957068 (**1c**), 1957070 (**1i**) and 1957069 (**1j**). For ESI and crystallographic data in CIF or other electronic format, see DOI: 10.1039/x0xx00000x

suffer from certain limitation such as harsh reaction condition, use of toxic agent, poor selectivity or poor atom economy.[22-23] So far, we are aware of only two examples for selective base- and oxidant-free acceptorless double dehydrogenation of primary amines. The first example, developed by Szymczak and co-workers, is implying a Ru^{II}-(NNN) pincer complex which highly favoured the nitrile pathway.[24] The second one, recently expose by our group, is describing the use of simple [Ru(*p*-cym)Cl_2]$_2$ as pre-catalyst.[25] The addition of a strong base was found necessary to achieve both high reactivity and selectivity for the Ru^{II}-pyrazole/*t*-BuOK catalytic system described by Bera and co-workers.[26] Very recently, the combination of an external base/hydride source (hexamethylenetetramine) and the [Ru(*p*-cym)Cl_2]$_2$ pre-catalyst, reported by Mathaiah et al., generate good nitrile selectivity even for benzylamine derivatives.[27] Finally, various well defined monodentate NHC-Ru catalysts have been developed by Mata *et al.* for this transformation albeit with moderate nitrile selectivity.[28]

In this context, we wondered if the straight formation of coordinatively more rigid cationic complexes using bidentate NHC ligands instead of triphenylphosphine could generate more active and robust catalysts. Among the different types of donor-functionalized NHC hybrids ligands (N, O, and P), S-functionalized NHCs still remain an undeveloped class of ligands.[10e, 29] Interestingly, thioether-functionalized NHCs, associated to transition metal (Cu,[30] Ni,[31] Pd,[32] Pt,[33] Rh[31a, 34] & Ru[34b]), have proven to be efficient in several catalytic system.[30-31, 32c, 32e, 32j, 32l, 33c] Among these, only one NHC-Ru(cym) thioether catalyst was reported and applies to the catalytic hydrogenation of styrene and 1-dodecene.[35]

Herein we report the synthesis of a series of bidentate thioether-functionalized N-heterocyclic carbenes precursors with various –SR substituents. The corresponding cationic NHC-ruthenium complexes were prepared from [Ru(*p*-cym)Cl_2]$_2$ generating exclusively chelate complexes with a κ^2-(*C*,*S*) coordination mode. The stereochemistry issue of complexes were studied by a combination of variable temperature (VT) ^{1}H-NMR experiments, X-ray diffraction studies and DFT calculations. Studies on the catalytic activity and selectivity of these NHC-Ru complexes have been conducted on the double dehydrogenation of amine without the use of any additional oxidant. Under optimized conditions, alkyl amines were transformed into nitrile with good selectivity. Finally, the cytotoxicity of relevant NHC-Ru complexes was evaluated on various cancer cell-lines.

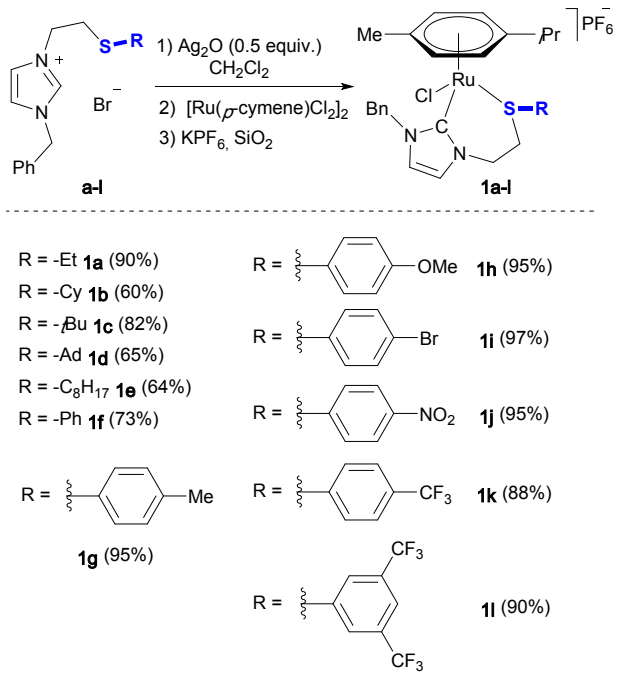
Results and discussion

Synthesis and characterization of the cationic *C,S*-chelated ruthenium complexes (1a-l)

The S-functionalized imidazolium precursors **a-l** have been synthesized in two steps starting from benzyl imidazole. Reaction of benzyl imidazole with 1,2-dibromoethane provided 1-benzyl-3-bromoethylimidazolium bromide, which was next quantitatively functionalized by reacting with the desired thiolate (see ESI for details). NHC-ruthenium complexes **1a-l** were obtained from corresponding imidazolium salts **a-l** by a classic transmetalation pathway between the silver-carbene intermediate and [Ru(*p*-cym)Cl_2]$_2$. Subsequently, the anion exchange between Br^- and PF_6^- was followed by purification by chromatography on silica gel to afford complexes **1a-j** in good yields (Figure 1).

All complexes were obtained as orange to dark orange microcrystalline powder and are air-stable in solid state. The formation of the [(NHC)Ru(p-cym)Cl][PF_6] complexes **1a-l** was established by the disappearance of the typical proton signal between δ 9–11 ppm assigned to the 2H-imidazolium in the ^{1}H NMR spectrum and also by the appearance of a signal between δ 165–170 ppm in the ^{13}C-NMR spectrum, which corresponds to the ruthenium carbene carbon. The analytical data (HRMS, ^{1}H-NMR) advocated for the coordination of NHC in a chelate κ^2-(C,S) fashion which was later unambiguously confirmed by X-ray analysis on single crystal (*vide infra*).[36]

Figure 1. Synthesis of cationic chelated ruthenium complexes **1a-l**.



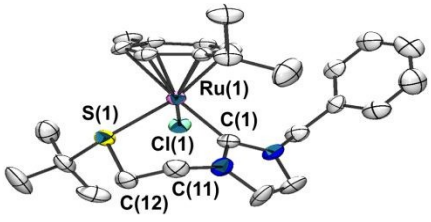
The ^{1}H-NMR spectra of all complexes compared to the spectra of imidazolium precursors display a marked difference in the region between 2.4 and 4.9 ppm which correspond to the -NCH_2CH_2S- moiety. This observation is consistent with ligands that bind in a κ^2-(C,S)-chelating fashion, rendering the -CH_2N- and -CH_2S- protons diastereotopic in the newly formed metallacycle. The signals of the two protons of each N-CH_2 and S-CH_2 are now split into two sets of two different multiplets. It is observed, for each case, that one of the methylene N-CH_2 and S-CH_2 protons is slightly deshielded while the other one is

strongly shielded compared to imidazolium precursor (Δδ +0.07/-0.8 ppm for S-CH_2 and Δδ +0.11/-0.65 ppm for N-CH_2). Surprisingly, instead of a complex diastereomeric mixture that would result of the presence of two stereogenic centers on the sulfur and the metal center and associated to possible dynamic processes namely sulphur inversion or its hemilability,[33a, 37,38] in all cases only one set of signals is observed in solution by the ^{1}H-NMR. The situation could be even more complicated considering the formation of the six-membered ring between metal and ligand whose different conformations could generate as well a dynamic process in solution.[39]

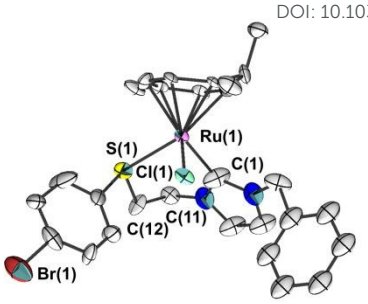
X-ray analyses

Single crystals suitable for X-ray diffraction analysis of **1c**, **1i** and **1j** were obtained by slow diffusion of diethyl ether into concentrated solution of complexes in dichloromethane (1/3). The molecular structure of the three complexes are depicted in Figure 2 along with key bond lengths and bond angles.[40] All these complexes display the expected three-legged piano-stool geometry around the ruthenium center. As a result of the coordination of the pro-chiral thioether, two stereocenters are present and consequently a diastereomeric mixture may be expected. For the three structures, only one enantiomeric pair ($R_{Ru}S_S$/$S_{Ru}R_S$) of complex was found in the solid state.[41] The R group of the thioether is oriented in *anti*-position with respect to the *p*-cymene ligand as a consequence of steric repulsions. This geometry forces the thioether to adopt a single configuration and thus disfavoured the formation of the enantiomeric couple $R_{Ru}R_s$/$S_{Ru}S_S$ in the solid state. The Ru-Carbene bond distance of complexes 1c, 1i and 1j are in the range of other NHC-Ru(p-cymene) complexes which are in between 2.02-2.09 Å.[8d, 13, 28, 34b, 35a, 42] Ru-S bond distances are in the range to those describe in the literature for thioether-Ru(p-cymene) complexes.[37f, 43] However, these bonds lengths are longer compared to the one observed for the two chelates NHC/thioether ruthenium complexes reported so far.[34b, 35a] Considering the standard deviation calculated for these Ru-Carbene and Ru-S bonds lengths (see figure 2), no significant differences can be drawn from these value. The larger value observed in complexes **1c-1i** for the <S-Ru-C> angle (89.1-90.3°) compared to 84.6° in complex **1j** is most likely related to the difference in conformation of the 6-membered chelate ring which is half-chair when R = *t*Bu or *p*-Br-C_6H_4 and boat conformation when R = *p*-NO_2-C_6H_4.

(a)



(b)



(c)

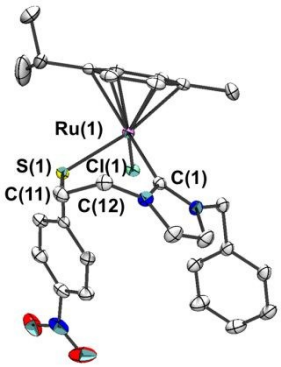


Figure 2. Molecular structure of ruthenium NHC complexes **1c**, **1i** and **1j**. Selected bond distances (Å) and angles (°): **1c** (a) CCDC n° 1957068 : Ru(1)-C(1), 2.075(7); Ru(1)-S(1), 2.398(2); R(1)-Cl(1), 2.407(2); Ru-Cym_{cent}(1.721); Cl(1)-Ru(1)-S(1), 95.27(7); S(1)-Ru(1)-C(1), 90.3(2); C(1)-Ru(1)-Cl(1), 86.8(2). **1i** (b) CCDC n° 1957070: Ru(1)-C(1), 2.050(2); Ru(1)-S(1), 2.384(4); R(1)-Cl(1), 2.395(3); Ru-Cym_{cent}(1.720); Cl(1)-Ru(1)-S(1), 91.2(1); S(1)-Ru(1)-C(1), 89.1(4); C(1)-Ru(1)-Cl(1), 87.6(4). **1j** (c) CCDC n°1957069 : Ru(1)-C(1), 2.059(1); Ru(1)-S(1), 2.389(1); R(1)-Cl(1), 2.4061(5); Ru-Cym_{cent}(1.724); Cl(1)-Ru(1)-S(1), 87.77(1); S(1)-Ru(1)-C(1), 84.62(4); C(1)-Ru(1)-Cl(1), 92.16(4).

DFT Calculation

All signals in the ^{1}H-NMR were sharp and well-defined which was not expected thinking about the possible dynamic isomeric mixtures in solution. These analyses suggest either that, in solution, these Ru-species might a display dynamic stereochemical rearrangement, or that the Ru complex formation is diastereoselective. In order to gather insight into the system, computational studies were conducted. Three substituents were chosen for this study (-*t*Bu, **1c**, -Ph, **1f** and -CF_3, labelled as $\mathbf{1_{CF3}}$). First, we optimized the R_{Ru}/S_S configuration corresponding to complex **1c** base on the solid state structure. Energy optimizations for **1c** and $\mathbf{1_{CF3}}$ were performed using the same starting point (See ESI for computational details). Optimized structures were also computed for the R_{Ru}/R_S diastereomers corresponding to the inversion of configuration at the sulfur atom. Such configuration was found more stable for complexes **1c** and $\mathbf{1_{CF3}}$ and slightly less stable for complex **1f** (Figure 3).

The next step, was the search of the inversion path at the sulfur atom throughout two possible processes: i) an intramolecular pyramidal inversion mechanism without bond rupture (Figure 3) or ii) a dissociative/associative mechanism (Figure 4). Both pathways were investigated and they are

discussed below. In addition, the influence of the substituents on the thioether group was also analyzed.

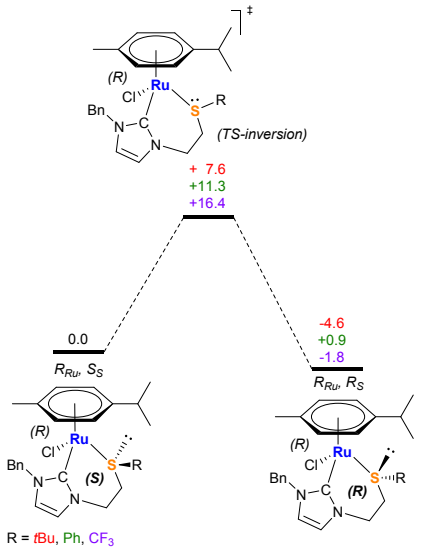


Figure 3. Calculated sulfur pyramidal inversion pathway for **1c** (red), **1f** (green) and $\mathbf{1}_{CF3}$ (black) (values in Kcal mol^{-1}. The PF_6^- anion was omitted for clarity).

The calculations established that sulfur inversion trough pyramidal inversion might be favored and relatively easy for S-*t*Bu and S-Ph groups ($+7.6 \leq \Delta G^{\ddagger} \leq +11.3$ kcal.mol^{-1}) (Figure 3) compared to the dissociative/associative pathway in which the second step, recoordination of the sulphur atom, is the limiting step of the reaction and an unfavorable process ($+15.8 \leq \Delta G^{\ddagger} \leq +18.2$ kcal mol^{-1}) (Figure 4).

Interestingly, this trend is reversed in the presence of the strong electron withdrawing group as $-CF_3$ for which the dissociative/associative pathway ($\Delta G^{\ddagger}$ = 6.1 kcal mol^{-1}) is now favored by more than 10.3 kcal mol^{-1} compared to the pyramidal inversion. The presence of this strong electron-withdrawing group at the sulfur atom further weakens the S-Ru bond favoring the dissociative/associative mechanism.

This counterintuitive result might be explained by the analysis of the Ru-S distances on the intermediate and TS2-coordination. The optimized geometry on the intermediate features Ru-S distances over 5 Å for R = *t*-Bu and Ph (5.51 Å and 5.20 Å, respectively) with the substituent placed far from the *p*-cym ligand in order to minimize steric hindrance. In the case of R = CF_3, the Ru-S distance is 4.92 Å and the substituent is closer to the *p*-cym ligand. The second step, TS2-coordination, model for R = *t*-Bu and Ph the shortening of the Ru-S distance by 1.97 Å (R = *t*-Bu) and 1.56 Å (R =Ph) plus the rotation of the substituent away from the *p*-cym ligand while R = CF_3 mainly model a shortening of 1.35 Å. This observation highlight that the re-coordination step seems to depend on both, the shortening of the Ru-S distance and the minimization of the steric hindrance between the substituent and the *p*-cym ligand being more demanding for R = *t*-Bu and Ph than for R = CF_3.

Overall, the calculations predict a fast and easy dynamic sulfur inversion, which is too fast for the NMR timescale at 298K what is coherent with the observation of only set of signals in solution by the ^{1}H-NMR which would correspond to an average signals of different species/isomers. Nevertheless, studies on the relative higher activation barrier computed for **1f** ($\Delta G^{\ddagger}$ = +11.3 kcal mol−1), suggests the possible experimental observation of two diastereoisomers by the variable temperature NMR (details discussed in the following section).

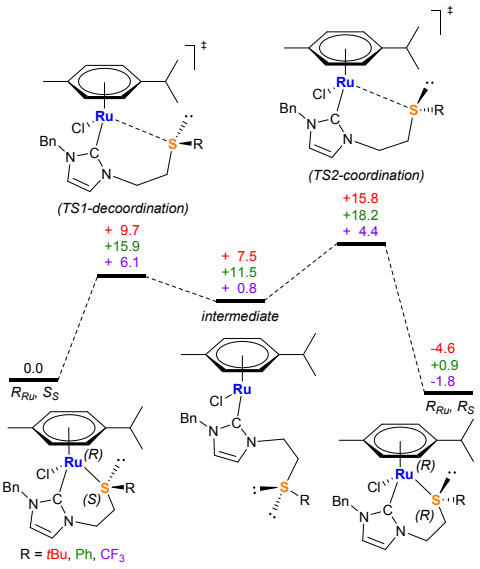


Figure 4. Calculated dissociative/associative pathway for **1c**, **1f** and $\mathbf{1}_{CF3}$ (values in Kcal mol^{-1}. The PF_6^- anion was omitted for clarity).

VT-NMR experiments

More insights in the possible dynamic processes were obtained by variable-temperature ^{1}H-NMR studies of the compounds in CD_2Cl_2 in the range of 298-198 K and in 1,2-dichlorobenzene-d_4 in the range of 298-378 K.

For complex **1c** (-*t*-Bu), increasing (up to 378 K) or decreasing (up to 198 K) the temperature did not display any additional signals. These results may indicate that compound **1c** has a fixed stereochemical arrangement around Ru without decoordination of the thioether, but with a low activation barrier for Sulphur inversion in agreement with the DFT calculations. In consequence, the variable-temperature ^{1}H-MR experiments of complex **1f** (-Ph) now display a different feature at low temperature. Four multiplets corresponding to the N-CH_2-CH_2-S chain which integrate for one proton and the CH_3 peaks of cymene integrating for three protons became broader as the temperature decreased and de-coalesced at 248 K, before splitting into sharp signals. At 193 K, we observed a 2/1 diastereomeric mixture and no triplet signals corresponding to uncoordinated thioether species were observed (see ESI for details). These results are consistent with the previous DFT calculations (see Figure 3). Finally, the free energy of activation ($\Delta G^{\ddagger}$) for this process based on the coalescence temperature of the SCH_2 group is of ca. 11.2 kcal mol^{-1} and 11.9 kcal mol^{-1} based on the CH_3 of the cymene group which is also in agreement with the theoretical studies (i.e. 11.3 kcal mol^{-1}, Figure 3).[44]

The low temperature VT-NMR was also carried out on complex **1l** which contains 2 $-CF_3$ withdrawing groups and could be

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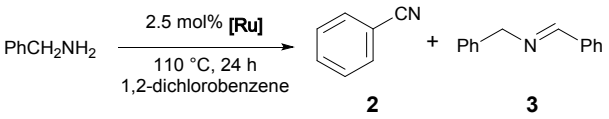
compared with the computed -SCF_3 group by the calculation. Once again, no de-coalescence was noticed even at 193 K for this complex. The only mechanism fairly consistent with experimental and theoretical data appears to be the pyramidal inversion without any Ru-S bond dissociation for both **1c** and **1f** complexes.

Application to catalysis: oxidation of primary amine to nitrile under oxidant free conditions

In a first set of experiments, the dehydrogenation of benzylamine into benzonitrile was chosen as benchmark reaction and complex **1c** was originally selected for optimizing the experimental conditions. The best conditions were obtained by varying the temperature, solvents and additives (See ESI table S1). Finally, the reactions were performed using 2.5 mol% of Ru-complex and 0.2 mmol of benzylamine in 0.2 mL of 1,2-dichlorobenzene (ODCB) at 110 °C in an open vessel under inert atmosphere. With this combination, high conversion was observed after 24h and the benzonitrile was generated as the major compound with some imine product both confirmed by the ^{1}H-NMR and GC analysis (see ESI table S1). Control experiments showed that in absence of the catalyst no reaction occurred and that only traces of imine were detected in a close system[8e] under these experimental conditions.[25, 45] In contrast to previous reports,[26-27], the presence of either weak or strong base have no or slight effect on both the nitrile/imine ratio and reactivity.[28]

The NHC-Ru complexes **1a-l** bearing thioether groups with different electronic and steric properties, that may affect coordination with the ruthenium center, were next evaluated under the optimized standard conditions (Table 1).[46] All cationic catalysts were found active generating a mixture of nitrile and imine products. Overall, it emerges that catalysts bearing an electron donating alkyl group are more active than those having aryl groups. Only the aryl-complex **1l** reaches the same level of reactivity of bulky alkyl type complexes (Entry 13).[47] The same trend was observed for the selectivity of the reaction for which complex **1c** (S-*t*Bu) displayed the highest nitrile ratio (Entry 3) and complex **1i** (p-Br) the highest imine ratio (Entry 10). Either, bulky or long alkyl chains have a detrimental effect on the formation of nitriles. In addition, aromatic substitutions by strong electron donating or withdrawing groups are both unpropitious for nitrile selectivity (Entries 8-13). Finally, alkyl groups with the strongest σ-donating power generate the nitrile as major product of the reaction (Entries 1-3).

Table 1. Evaluation of benzylamine oxidation in presence of NHC-Ru complexes.[a]



2 **3**

Entry	Ru	R^1	R^2	Conv. (%)[b]	Selectivity (%)[b] **2**	**3**
1	**1a**	Et	Bn	77	55	45
2	**1b**	Cy	Bn	92	57	43
3	**1c**	*t*-Bu	Bn	90	60	40
5	**1d**	Ad	Bn	90	50	50
6	**1e**	*n*-Oct	Bn	84	48	52
7	**1f**	Ph	Bn	89	40	60
8	**1g**	*p*-Me(C_6H_4)	Bn	88	50	50
9	**1h**	*p*-OMe(C_6H_4)	Bn	70	40	60
10	**1i**	*p*-Br(C_6H_4)	Bn	72	37	63
11	**1j**	*p*-NO_2(C_6H_4)	Bn	72	44	56
12	**1k**	*p*-CF_3(C_6H_4)	Bn	88	54	46
13	**1l**	*3,5*-CF_3 (C_6H_3)	Bn	92	50	50
14	**4**	*t*-Bu	CH_3	98	65	35
15	**5**	*t*-Bu	CH_3	90	39	61

[a] Reaction conditions: benzylamine (0.2 mmol), 2.5 mol% cat. based on Ru and 1,2-dichlorobenzene (0.2 mL), 110 °C, 24h, open vessel under argon atmosphere; [b] Conversion and selectivity were determined by ^{1}H RMN hexadecane as internal reference.

In the dehydrogenative amidation of alcohol and amine catalyzed by NHC-Ru systems, it has been shown that the reactivity and the selectivity are sensitive to the N-substitution[7a, 7b] of the NHCs and that benzimidazole[8g, 8k, 8l, 9] core displays often better activity than imidazole counterpart. A second generation catalysts were synthesized and evaluated, under our catalytic conditions, to address these two points (Figure 5). First, steric effect on the nitrogen of the NHCs was assessed through the complex **4**, which has a methyl group instead of the benzyl group. The catalyst showed the highest reactivity and selectivity (entry 14). Secondly, the corresponding benzimidazole complex **5** also promotes this transformation but in contrast to its imidazole analogue **1c**, catalyst **5** favors the formation of imine rather than nitrile products (Entry 15). This outcome indicates that the electron-donating properties of the NHCs are crucial for imparting high selectivity of nitrile. This observation is in the line of a recent publication which uses a strong electron-donating Ru^{II}-(1,2,3-triazolyllidene-pyridine) bidentate complex system in the presence of both O_2 and NH_3.[48]

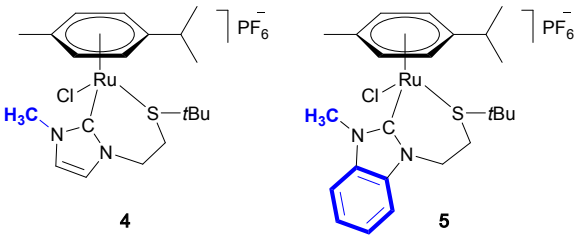
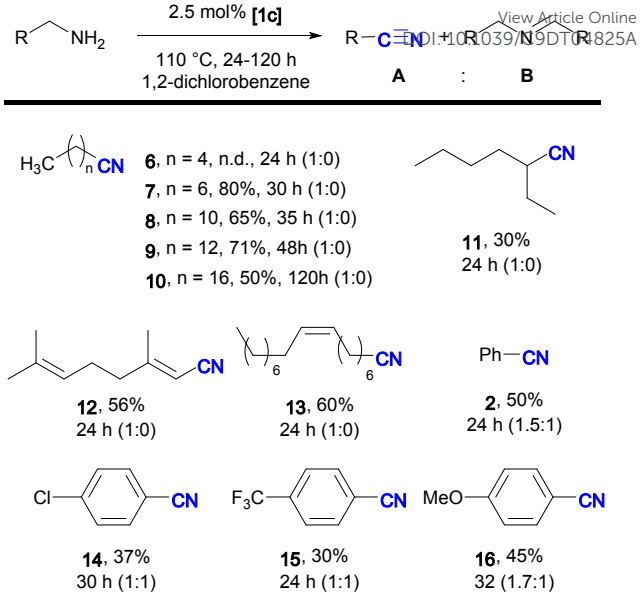


Figure 5. Steric and electronic variations: molecular structure of complexes **4** and **5**.

We then decided to further use complex **1c** to investigate the scope and limitations of the catalytic double dehydrogenation of primary amines (Figure 6). On primary amines, irrespective of the nature of the alkyl chain (long, branched or saturated), the formation of the corresponding nitrile was formed exclusively. Thereby good yields were obtained after purification on SiO_2. Substrates with unsaturated alkene functions were also used and the corresponding products were obtained in good yield. However the kinetic of the reaction was dependent on the length of the alkyl chain; for example the octadecylamine required 120 h of reaction time to achieve full conversion. Benzylamine derivatives were also investigated albeit with low selectivity and formation of imines. Electron-rich benzylamine derivative **16** showed the best nitrile selectivity compared to electron-poor substrates. Consequently the lower yields obtained for these benzylic derivatives are mainly due to poorest selectivity and also issues during the purification step.[49] Globally, these results show the difficulty to control the factors that govern the selectivity of the reaction with benzylamine derivatives. The uses of several NHC-S ligands were found quasi-ineffective for the discrimination of the two products formed. Even if those cationic complexes display slight better nitrile selectivity for aliphatic amines than neutral monodentate NHCs their presence on the coordination sphere of the metal inhibit somehow the catalytic reactivity and selectivity compared to the simple $[Ru(p\text{-cym})Cl_2]_2$ complex.[25, 27] However Szymczak showed that the presence of an appropriate ligand on ruthenium could achieved, under oxidant-free conditions, high level of both reactivity and selectivity for activated amines.[24] Therefore, further efforts onto the design of more active and selective ligands are thus required for such challenging substrates.

Figure 6. Reaction scope of primary amines double hydrogenation with catalyst **1c**.[a]



[a] Isolated yields; A:B ratio in parenthesis.

To gain more insight into the reaction mechanism, an equimolar mixture of benzylamine and complex **1c** was dissolved in CD_2Cl_2 at room temperature, and followed by the ^{1}H-NMR experiments. Interestingly, the spectra displayed no change after 24 hours, even in the presence of 10 equivalents of amine and heating up to 60 °C for 6 hours. In order to be closer than the reaction conditions, complex **1c** was heated at 110 °C in the presence of two equivalents of benzylamine in deuterated ODCB (in a closed system). After two hours no changes were observed. Interestingly however after longer time (18 h), free cymene was identified with a ratio Ru-*p*-cym/free cym of 4/1 in solution. When the reaction was set up with ten equivalents of benzylamine at 110 °C for 24 h, we observed an almost complete dissociation of the cymene (see ESI fig. S13),[50] and the NHC ligand remained attached to the metal center (see ESI). This observation, in line with previous reports, indicates that the *p*-cymene complex is probably not involved in the catalytic cycle.[8f, 9, 13, 48] Even if, no clear evidence of amine coordination was detected in the ^{1}H-NMR spectrum, the observation of imine suggests that this process should take place (see ESI). In the presence of the only imine product and the ruthenium complex **1c**, under our standard conditions, no reaction occurred after 24h.

To avoid the dehydrogenation pathway the *tert*-octylamine, which cannot undergo the elimination process, was also used. Once again, no displacement of either -S*t*Bu or Cl^- was observed even after 24h at 110 °C in ODCB, suggesting that the starting complex is a highly stable resting state.

In vitro activity of selected Ru NHC complexes

Ruthenium complexes are of great attention in the development of metal-based anticancer compounds.[51] Some ruthenium(II) *p*-cymene have shown good antiproliferative activities against various cancer cell lines and also low systemic

toxicity.[51] In addition, N-heterocyclic carbene ligands are of particular interest in the field of medicinal inorganic chemistry.[33d, 52] They allowed generating robust complexes even in the presence of water and they fit many prerequisites for easy optimization.

Antiproliferative activities of some representative ruthenium complexes described here, namely **1a**, **1d**, **1f** and **1l**, were measured on a panel of three different human tumor cell lines (namely MCF7, HCT116 and PC3) (IC_{50}, Entries 1-4, Table 2). Complexes **1a** (-Et) and **1f** (-Ph) displayed activities in the range 50-75 µM. On the other hand, complexes **1d** (-Ad) and **1l** (-3,3'-CF_3-C_6H_3) showed good activities (up to 3.5 µM). These results are most likely connected with the lipophilicity[53] of the complexes since adamantane[54] or fluorine-containing[55] substituents are known to enhance the overall lipophilicity of the molecule. Since the mode of action is not yet known, the steric bulk might be as well a potential factor that influences the cytotoxicity observed. Indeed, it also appears that increasing the steric bulk of the substituent at sulfur atom increases activity.

Table 2 Half inhibitory concentrations IC_{50} (in µM) of the selected Ru compounds against human cancer cell lines.[a]

Entry	Compound	HCT116	MCF7	PC3
1	**1a**	56.9±11.2	75.9±3.05	74.3±10.8
2	**1d**	4.90±0.19	14.3±0.94	3.54±0.23
3	**1f**	49.1±1.77	57.2±6.96	65.7±13.8
4	**1l**	9.79±0.19	12.8±2.23	10.01±1.02

[a] after 72 h of incubation; stock solutions in DMSO for all complexes.

Stability in solution of the compounds is an important requirement in medicinal chemistry. Because solutions were prepared in DMSO/water, these results should be correlated with the stability of the ruthenium complexes in solution, which could easily be monitored by the ^{1}H-NMR or UV-vis. Investigation of the complexes stability by the ^{1}H-NMR in a 1/1 mixture of dmso-d_6 and D_2O, revealed no change after 4 days and the complexes remained intact.

Conclusions

In summary, we have developed a variety of well-defined thioether-functionalized N-heterocyclic carbene (κ^2-C,S)-Ru(II) η^6-cymene cationic Ru complexes by varying the substituents of the thioether. Surprisingly the crystallographic analysis display only one ruthenium specie as an enantiomeric couple rather than the expected diastereomeric mixture. Despite this, a very fast sulphur inversion at room temperature was established by a combination of VT ^{1}H-NMR experiments and DFT calculations which might account for a dynamic stereochemical rearrangement which would be responsible to the presence of fluxional mixtures at room temperature as observed by the ^{1}H-NMR spectroscopy. In addition these calculations indicated that donating groups on the sulfur atom favored the intramolecular pyramidal inversion mechanism while electron withdrawing group favored the dissociative/associative pathway. Through a systematic investigation of the ligand structures and various reaction conditions, the cationic ruthenium complex **1c** was found to be the most active catalyst for the double dehydrogenation of primary amine to give the corresponding nitrile under oxidant- and base-free conditions. With these bidendate NHCs, high selectivity has been achieved using aliphatic amines and only a poor to no selectivity was obtained with benzylamine derivatives. Investigation on the active species clearly indicated the decoordination of *p*-cymene. Finally, these ruthenium complexes showed promising cytotoxic activities on several human cancer cells. We are currently further evaluating their biomedical properties varying the nature and the complexity of the systems in order to improve the cytotoxic profile and selectivity of the resulting complexes.

Conflicts of interest

There are no conflicts to declare.

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41 Modified CIP rules were used, here the polyhapto ligand (*p*-cym) is considered pseudo-atoms of atomic weight equal to the sum of the atomic weights of all the atoms bonded to the metal atom (molecular weight 72). As a consequence, the following priority sequence applies for all complexes: η^6-*p*-cymene > Cl > S > C_{Carb}. For more information see : (a) C. Lecomte, Y. Dusausoy, J. Protas, J. Tirouflet and A. Dormond, *J. Organomet. Chem.*, 1974, **73**, 67-76 (b) K. Stanley, M. C. Baird, *J. Am. Chem. Soc.*, 1975, **97**, 6598-6599. (c) E. B. Bauer *Chem.Soc.Rev.*,2012, **41**, 3153-3167.

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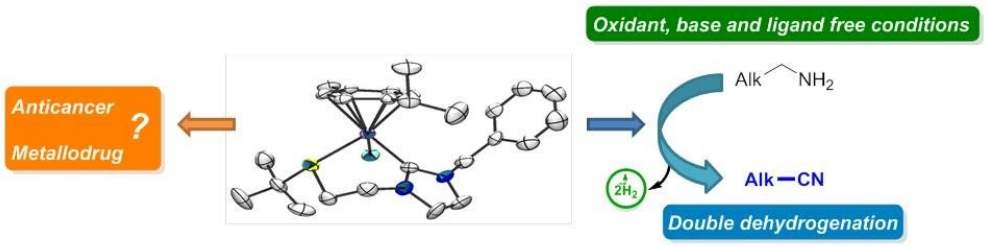

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