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Diastereoselective Synthesis of Sulfoxide-Functionalized N-Heterocyclic Carbene Ruthenium Complexes: An Experimental and Computational Study.

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Supporting information for this article is given via a link at the end of the document.

Abstract: The synthesis of sulfoxide-functionalized NHC ligand precursors were carried out by direct and mild oxidation from corresponding thioether precursors with high selectivity. Using these salts, a series of cationic $[\text{Ru}(\text{II})(\eta^6\text{-}p\text{-cymene})(\text{NHC-SO})\text{Cl}]^+$ complexes were obtained in excellent yields by the classical Ag_2O transmetallation route. NMR analyses suggested a chelate structure for the metal complexes, and X-ray diffractometry studies of complexes **4b**, **4c**, **4d_{BARF}** and **4e** unambiguously confirmed the preference for the bidentate ($\kappa^2\text{-C,S}$) coordination mode of the NHC-SO ligands. Interestingly, only one diastereomer, in the form of an enantiomeric pair, was observed both in ^1H NMR and in the solid state for the complexes. DFT calculations showed a possible intrinsic energy difference between the two pairs of diastereomer. The calculated energy barriers suggested that inversion of the sulfoxide is only plausible from the higher energy diastereomer together with bulky substituents. Inverting the configuration at the Ru center instead shows a lower and accessible activation barrier to provide the most stable diastereomer through thermodynamic control, consistent with the observation of a single species by ^1H NMR as a pair of enantiomers. All these complexes catalyse the β -alkylation of secondary alcohols. Complex **4d_{PF6}** bearing an NHC-functionalised S-Ad group has been further studied with different primary and secondary alcohols as substrates, showing high reactivity and high to moderate β -ol-selectivities.

The construction of a C-C bond is one of the fundamental reactions of organic chemistry. This will make it all the more important to research and develop environmentally-friendly processes for this type of reaction. In industry, alcohols represent one of the main intermediate compounds used, mainly for two reasons: (i) these lignocellulosic raw materials are available and bio-renewable^[1] (ii) they can be converted into essential functionalized compounds.^[2] This is why readily available alcohols from renewable resources have attracted particular attention as alkylating agents or electrophiles for building single C-C bonds. In this context, the β -alkylation of secondary alcohols via the hydrogen borrowing strategy appears to be an environmentally friendly method of choice for the production of higher alcohols.^[3] The last two decades have seen the emergence of numerous Ru-catalyzed cross-coupling reactions between secondary and primary alcohols, leading to one-pot tandem β -alkylation through oxidation/cross-aldol condensation/hydrogen transfer sequence.^[3a] Since the report of Cho with the $\text{RuCl}_2(\text{PPh}_3)_2$ catalyst,^[4] series of several ligand families (pincer, tridentate, bidentate) have been developed to produce improved catalysts.^[3b] These studies highlighted the fact that the ligand environment around the metal center significantly influences the catalytic activity of ruthenium complexes.

N-heterocyclic carbene ligands are attracting increasing interest, not least because of the ease with which their electronic and steric properties can be tuned.^[5] One of the main properties of NHCs is their strong σ -donor capacity toward transition metals,^[6] making them a strong anchor point for the metal center while enabling the stabilization of transition metals in organometallic chemistry and homogenous catalysis.^[7] Therefore, the development of new

Introduction

NHCs scaffolds is still an area of growing interest.^[5b, 7] Among these modifications, a strong interest was turned on NHC-hybrid ligand functionalized by several potentially hemilabile^[8] heterodonor atoms predominantly N, O or P.^[9] On the other hand, S-functionalized NHCs are still a relatively underdeveloped family of ligands that have recently attracted a great deal of attention.^[10] Different sulfur-functionalized NHC complexes bearing thiolate, thioether, sulfoxide, sulfone, sulfonate, and thiophene groups have been reported.^[10] Due to the prochirality,^[11] and the hemilability^[12] of the thioether group coupled to the ease of introduction of chiral moieties,^[13] thioether-NHC (abbreviated NHC-SR) family has been the most studied in the last fifteen years. Combined with different transition metals (Au,^[14] Cu, Ir,^[13a] Pd,^[13b, 15] Pt,^[12c, d] Rh^[16] & Ru^[16a, 17]), these NHC-SR have enabled a number of interesting catalytic transformations.^[10c, 18] Curiously, only rare examples of NHC-sulfoxide were reported in the literature, and some of their metal complexes (Au, Cu and Pd) have been evaluated in various catalytic reactions.^[19]

It was first described by Peris *et al.* that, combined with ruthenium, N-heterocyclic carbene (NHC) ligands are good partners to catalyze the β -alkylation of secondary alcohols with primary alcohols.^[20] Since then, only a limited number of ruthenium-NHC complexes have been reported in the literature,^[20-21]

Recently, our group has shown that Ru cationic complexes of NHC functionalized with thioethers are able to selectively catalyze the β -alkylation of secondary alcohols with primary alcohols.^[21] Precise studies carried out on these NHC-SR Ru complexes have revealed that a very rapid inversion of sulfur takes place at room temperature, which leads to a dynamic stereochemical rearrangement responsible for the presence of fluxional mixtures of isomers.^[22] Therefore, we wondered whether locking the sulfur atom by the addition of an oxygen atom, through thioether oxidation, would generate better stereo-defined complexes and then potentially increase their catalytic activity and selectivity.

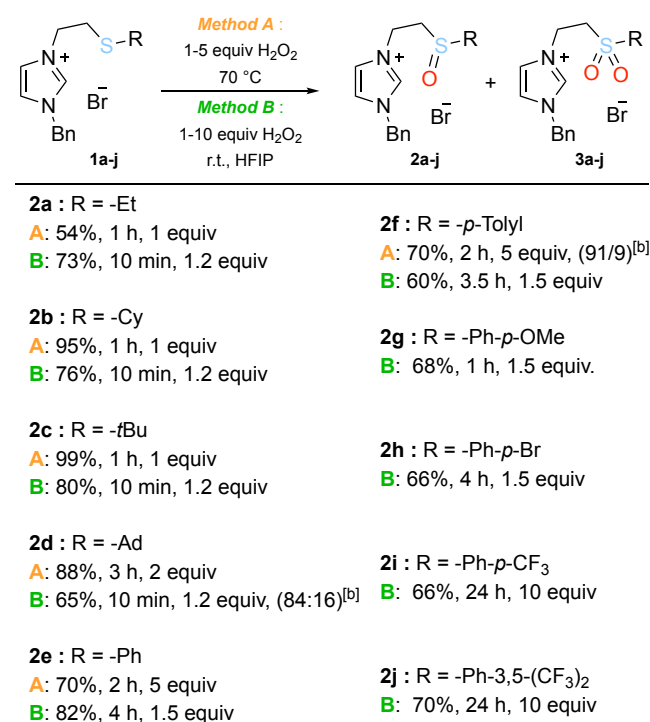
Herein we report the preparation of a series of bidentate NHC-SO precursors, with various -SR substituents, via green and selective oxidation of NHC-SR with H₂O₂. The corresponding cationic (NHC-SO)-ruthenium complexes were prepared from [Ru(*p*-cym)Cl₂]₂ generating exclusively chelate complexes with a κ^2 -(C,S) coordination mode. The reaction was diastereoselective generating only one diastereomer as a couple of enantiomers. The stereochemistry issue of complexes was studied by a combination of variable temperature (VT) ¹H-NMR experiments, X-ray diffraction studies and DFT calculations. Finally, the catalytic activity of these NHC-Ru complexes was successfully evaluated in the β -alkylation of primary and secondary alcohols through dehydrogenative coupling processes.

Results and Discussion

Synthesis and characterization of the NHC-SO ligands (1a-j)

Functionalized imidazolium salts NHC-SR **1a-j** were prepared (except **1e**) according to our previously reported two-step procedure from benzyl imidazole followed by nucleophilic

substitution of bromine with the desired commercial or in situ generated sodium thiolate.^[12d, 22-23] To prepare NHC-SO **2a-j** ligands, several metal-free oxidation conditions were evaluated on imidazolium **1c**. The SO₂Cl₂/wet silica,^[24] H₂O₂/CH₃CN^[25] or H₂O₂/AcOH^[19a, 26] oxidation systems all led to undesirable partial or total overoxidation of thioether **1c** to sulfone **3c** (Table S1 in the SI). In contrast, the solvent-free H₂O₂ method developed by Beller *et al.* showed high selectivity for the formation of sulfoxide **2c**.^[27] This environmentally-friendly protocol only involved one equivalent of hydrogen peroxide in presence of 1 equivalent of the NHC-SR at 70 °C for one hour (calls *method A*). This reaction proceeds well and is highly chemoselective for the alkyl-thioether NHCs derivatives giving only the sulfoxide product in moderate to good yields (*method A* figure 1). Unfortunately, increasing this reaction to 1.4 mmol of **1c** required a longer reaction time which generated 14% NHC-sulfone, resulting in a complicated and time-consuming chromatographic purification (see Table S1 in the SI). However, bulky and lipophilic adamantyl group, requires longer reaction time, small excess of H₂O₂ as well as a small amount of DCM^[28] to achieve high conversion and selectivity (figure 1). For aryl derivatives, in contrast, the reaction is much slower and therefore requires more equivalents of H₂O₂ to complete, resulting in a loss of reaction selectivity.



^[a] 0.35 mL of HFIP; 0.1 g of compound **2**. ^[b] Conversion and ratio of products **2/3** were determined by ¹H-NMR.

Figure 1. Synthesis of imidazolium sulfoxide-functionalised NHC-SO from **1a-j** precursors, using hydrogen peroxide (isolated yields).^[a,b]

To circumvent this overoxidation processes we used 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), as described by Bégué and co-workers.^[29] The electron-withdrawing character of the CF₃ group promotes strong hydrogen bonding leading to two different roles

namely the activation of H₂O₂ and the decrease of the nucleophilicity of sulfur atom of the sulfoxide preventing its overoxidation.^[29b] This mild oxidation in neutral conditions was carried out in HFIP with 30% aqueous H₂O₂ at room temperature and after 10-15 min gave the corresponding alkyl sulfoxide as the sole product in good yields (70-88%, *method B*, figure 1), with the exception of the adamantyl derivative for which the formation of sulfone **3d** was still observed.

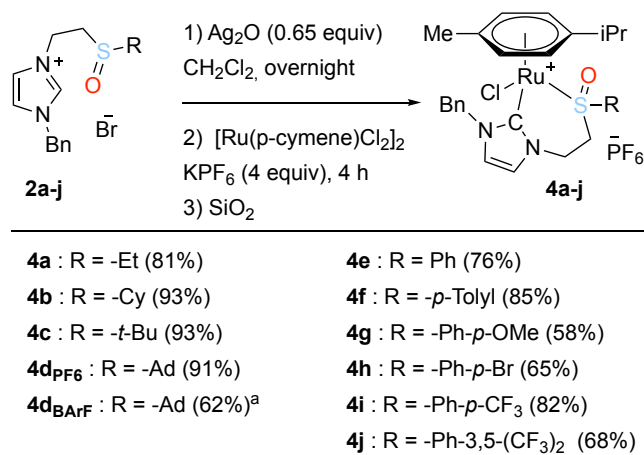
With *method B*, the same trend was observed for aromatic thioethers, which exclusively generated the mono-oxidised product, but with a longer reaction time (up to 24 hours). Phenyl substituents maintain high selectivity but affect the reaction rate, while an electron-donating group speeds up the reaction (4h for **2e** vs. 1h for **2g**), and electron-withdrawing group slows the process considerably (4h for **2e** vs. 12h for **2i-j**) and requires the use of a large excess of oxidant (5-10 equiv., *method B* see figure 1, entries **2i** and **2j**). Finally, compared with other procedures described in the literature for the synthesis of NHC-SO,^[19] this HFIP method offers a wide range of sulfoxide functions.

Before oxidation, the S atom is pro-chiral, so that the protons of N-CH₂ and S-CH₂ are homotopic, both showing a triplet form (at about 3.0 ppm and 4.5 ppm) in the ¹H-NMR spectra. After oxidation, the S atom of the sulfoxide becomes chiral, so that the protons of N-CH₂ and S-CH₂ are now diastereotopic. ¹H-NMR analyses showed that the two triplet signals of ethylene bridge were transformed into four sets of multiplet signals after oxidation, with values range around 3.0-3.5 and 3.6-4.3 ppm for the S-CH₂ protons and around of 4.5-4.9 and 4.6-5.1 ppm for the N-CH₂ protons.

Synthesis and characterization of the cationic κ²-(C,S)-chelated ruthenium complexes (**4a-j**)

With these NHC-SO ligands in hand, a new family of NHC-ruthenium **4a-j** complexes was synthesized via the classical two steps silver transmetallation route starting from imidazolium salts.^[23a] However, using this procedure, complexes **4a-j** were obtained in moderate to good yields (46–70%, Table S2 in SI), contrasting with the good yields obtained for their thioether counterparts.^[23a] A prolonged reaction time (12h) did not improve the yields and proved detrimental, leading to partial decomposition of the NHC-SO complexes (the solution turned from yellow to green), which may explain the lower yields obtained. Fortunately, this problem can be circumvented by adding excess KPF₆ (5 equiv.) directly during the transmetallation step, resulting in higher yields of up to 93% and without significant decomposition (Figure 2).

All complexes were obtained as orange powders after purification by silica chromatography.^[30] The formation of the [(NHC)Ru(p-cym)Cl][PF₆] complexes **4a-j** was established by the disappearance of the typical 2H-imidazolium proton signal between δ 9–11 ppm. The analytical data (HRMS, ¹H-NMR) advocated for the coordination of NHC in a chelate fashion which was later unambiguously confirmed to be κ²-(C,S) by X-ray analysis on single crystal (*vide infra*).



^a NaBArF was used instead of KPF₆ in the second step

Figure 2. Synthesis of cationic chelated NHC-SO ruthenium complexes **4a-j**.

The coordination of the sulfoxide moiety is evidenced by the downfield shift of the -CH₂- signals of the newly formed ring. Compared to the free ligands **2a-l**, for the region between 2.4 and 4.9 ppm which corresponds to the -NCH₂CH₂S- fraction in the ¹H-NMR spectra, we observed shielding of these protons around Δδ_H -0.1/-0.5 ppm for S-CH₂ and Δδ_H -0.3/-0.5 ppm for N-CH₂. These high-field chemical shifts of α-protons are quite unusual after sulfoxide coordination.^[31] This is probably due to the anisotropy of *p*-cymene, which exerts strong shielding through space for these α-protons. The IR stretching frequencies of ν_{SO}, **4a-j** complexes, range from ν_{SO} = 1054-1117 cm⁻¹, this increase in the ν_{SO} band relative to the free ligand (ν_{SO}=1023-1062 cm⁻¹) appears to be in agreement with S-coordination over O-coordination (see Table S6 in SI).^{[32][33]}

The presence of two stereogenic centers for these complexes on the sulfur and the metal center should generate at least a mixture of two diastereomers for each κ²-(C,S) (see figure 3) or κ²-(C,O) coordination mode of the sulfoxide group. The situation could be much more complicated due to the hemilability^[19c] of the sulfinyl group and the presence of different six- or seven-membered conformers, either of which could generate dynamic processes in solution.^[34] However, the ¹H-NMR spectra display only one set of very sharp and well-defined signals that always belong to a single species in solution. In no case broadened signals, resulting from possible dynamic processes, were detected in solution at room temperature (see Figure 4). Furthermore, energetically unfavorable O-coordinated 7-membered complexes, as well as S- or O-bridged species, have never been observed by NMR. As representative example, the pair of diastereoisomers for complex **4** κ²-(C,S)-coordinated are depicted in Figure 3.

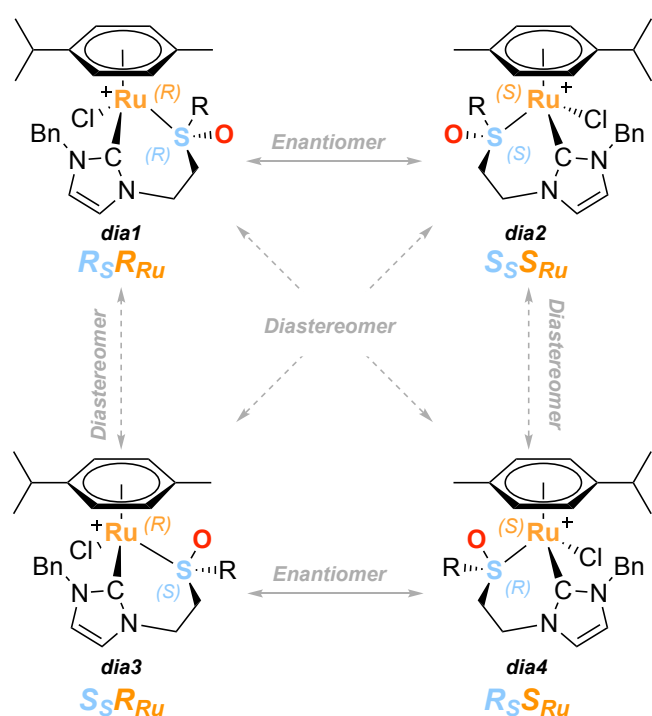


Figure 3. Description of the pair of diastereomers for κ^2 -(C,S) coordination of complex **4** (PF_6^- anion is omitted for clarity).

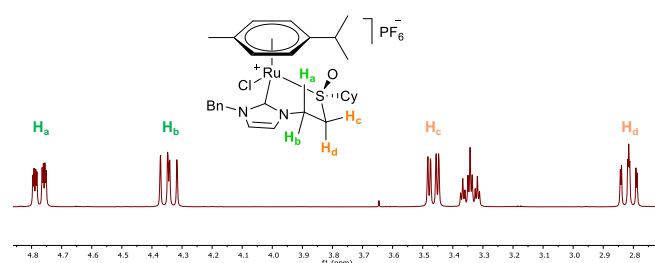


Figure 4. Assignment of the methylene protons in the $^1\text{H-NMR}$ spectrum of complex **4b**: ABCD system (Solvent: CDCl_3).

X-ray analyses

Single crystals suitable for X-ray diffraction analysis of compounds **4b-e**,^[35] were obtained by slow diffusion of diethyl ether into concentrated solution of complexes in acetonitrile. The molecular structure of the four complexes are depicted in Figure 5 along with key bond lengths and bond angles. All these complexes exhibit a three-legged piano-stool geometry around the tetrahedral Ru(II) centre. In each case we observed the coordination to Ru through the sulfur atom of the sulfoxide group confirming what is reported in the literature that the S-bonding mode seems to be largely favored for Ru complexes.^[32a-c, 34a] Although a diastereoisomeric mixture may be possible due to the presence of a new stereocenter arising from the coordination of the chiral sulfoxide. For the structures **4b-e** only one enantiomeric

pair ($R_{\text{Ru}}S_{\text{S}}/S_{\text{Ru}}R_{\text{S}}$) of complex was found in the solid state.^[36] The substituent group of the sulfoxide is oriented in the *anti*-position and the oxygen in the *syn*-position with respect to the *p*-cymene ligand. This can be induced by a probable combination of steric repulsions between the *p*-cymene and the S-R group but also by an electrostatic repulsion between the two strongly electronegative O and Cl atoms.

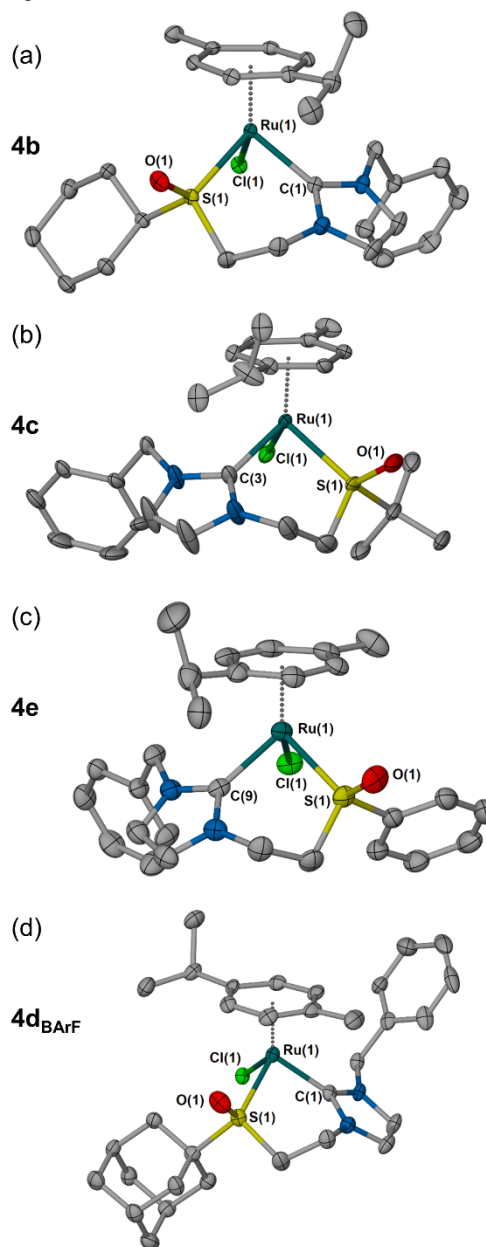


Figure 5. Molecular structure of ruthenium NHC complexes **4b**, **4c**, **4e** and **4d_{BarF}**. Anions are omitted for clarity. Selected bond distances (Å) and angles ($^\circ$): (a) **4b** C(1)-Ru(1) 2.046(2); S(1)-Ru(1) 2.2850(5); S(1)-O(1) 1.479(1); Cl(1)-Ru(1) 2.4053(3); Ru-Cym_{cent} (1.744); Cl(1)-Ru(1)-S(1) 89.39(2); S(1)-Ru(1)-C(1) 90.30(5); C(1)-Ru(1)-Cl(1) 85.99(5). (b) **4c** C(3)-Ru(1) 2.043(5); S(1)-Ru(1) 2.326(1); S(1)-O(1) 1.478(4); Cl(1)-Ru(1) 2.389(1); Ru-Cym_{cent} (1.741); Cl(1)-Ru(1)-S(1) 93.24(5); S(1)-Ru(1)-C(3) 90.16(2); C(3)-Ru(1)-Cl(3) 87.49(1). (c) **4e** C(9)-Ru(1) 2.057(4); S(1)-Ru(1) 2.299(1); S(1)-O(1) 1.473(3); Cl(1)-Ru(1) 2.374(1); Ru-Cym_{cent} 1.746; Cl(1)-Ru(1)-S(1) 90.90(4); S(1)-Ru(1)-C(9) 89.63(1); C(9)-Ru(1)-Cl(3) 86.16(1). **4d_{BarF}** C(1)-Ru(1) 2.045(5); S(1)-Ru(1)

2.3719(13); S(1)-O(1) 1.481(4); Cl(1)-Ru(1) 2.4045(12); Ru-C_{ym}cent 2.22; Cl(1)-Ru(1)-S(1) 93.50(4); S(1)-Ru(1)-C(1) 90.06(14); C(1)-Ru(1)-Cl(1) 89.80(13).

This geometry forces the sulfoxide 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. These results allow us to better assign this specific ABCD pattern (for S-CH₂CH₂-N) in the ¹H-NMR spectra which is defined by the enhancement of "conformational rigidity" imposed by bulky and electrostatic groups. The ³J_{HH} vicinal coupling constants measured in solution are in the same range as those predicted from dihedral angles measured in the solid state which allowed us to assign these resonances more accurately, as shown for complex **4b** in Figure 4.

The Ru-Carbene bond distance of complexes **4b-e** are within the range of other NHC-Ru(*p*-cymene) chelate complexes which are in between 2.02-2.09 Å.^[16a, 17, 21e, 37] However, the Ru-C bond of **4c** (2.043(5) Å) is slightly shorter than its sulfide analogue (2.075(7) Å).^[23a] Ru-S bond distances are in the range to those describe in the literature for sulfoxide-Ru(*p*-cymene) complexes (2.22-2.32 Å).^[38] The Ru-S_{sulfinyl} bond (2.326(1) Å, **4c**) is shorter than the Ru-S_{sulfide} bond (2.398(2) Å) for the corresponding NHC-SR,^[23a] which is consistent with literature data reported for the other S/SO ligand families.^[38c] Furthermore, the Ru-S bond distance is slightly elongated for the Ru-S-*t*Bu complex **4c** (2.326 Å) and significantly more for the **4d_{BAF}** (2.371 Å) complex compared to **4b** and **4e** (2.285 Å and 2.299 Å). This is probably linked to the higher steric constraints imposed on the molecule by the crowding of the *t*Bu and adamantyl groups. The S-O bond distances for these complexes are in the range of values reported for S-bonded ruthenium complexes (i.e., 1.473-1.481 Å) and therefore consistent with a double bond character.^[32a, b] For these tetrahedral Ru complexes the S-O bond distances are almost similar to the one recently reported for an octahedral NHC-SO ruthenium complexes (1.48-1.49 Å).^[19e] C-S-C and C-S-O angle of complexes **4b-e** average around 101.27° and 106.45° respectively are consistent with reported values for S-Ru complexes (99.2°; 106.22°).^[32a, b] In fact, this trend confirms the tetrahedral environment of the metal coordinated sulfur atom.

The 6-membered chelate rings of complex **4b,c,e** and **4d_{BAF}** in accord with their torsion angle values, all exhibit distorted half-chair conformations.^[39] The presence of the larger group (i.e., adamantyl) had a significant impact on the Ru-S (2.37 Å) and the Ru-cymene centroid (2.22 Å) bond lengths, which showed significant elongation compared with the other complexes.

Hemilability studies

The hemilability of the Ru-S bond was tested with complexes **4a** and **4d** due to the large steric difference between their sulfur

substituents (R = Et and Ad, respectively). No solvent-sulfoxide exchange was observed in any case (acetone-*d*₆, dms-*d*₆ and CD₃CN) and even the addition of PPh₃ for more than 24 hours didn't show any ligand exchange at the NMR timescale (Figures S8-17). In both cases, the sulfinyl group is still well bonded to the Ru atom. This lack of solvent exchange can be explained by the enthalpy penalty paid by the intermolecular exchange *versus* the intramolecular coordination of the sulfoxide moiety. In fact, calculations confirmed a small destabilization for the coordination of one CH₃CN solvent molecule. The binding of a PPh₃ ligand (R = *t*Bu) was also calculated to be uphill which is consistent with experimental observation.

DFT Calculations

As observed for the thioether complexes,^[22] all the ¹H NMR signals are also sharp and well defined for the NHC-SO, which was not expected given the possible dynamic isomeric mixtures in solution (hemilability, ambidentate behavior). These NMR analyses suggest two main hypotheses, (i) these Ru species may exhibit dynamic stereochemical rearrangement, (ii) or that the formation of the Ru complex is diastereoselective. To gain a better understanding of the system, computational studies were carried out.

With the aim of finding potential interconversion pathways between diastereomers in the reaction conditions for their preparation, the complexes bearing a *tert*-butyl-substituted sulfoxide **4c** and a phenyl-substituted sulfoxide **4e** were examined. Initial calculations on the diastereomer pairs immediately revealed a significant difference in relative stability depending on the orientation and configuration of the sulfoxide moiety. In both cases, the thermodynamically favored isomer features the oxygen pointing towards the *p*-cymene and the R substituent sterically removed from it. The free energy difference is more marked for the *t*Bu (7.8 kcal/mol) compared to the Ph analogue (2.3 kcal/mol) and was attributed to the steric buttressing occurring between the R group and the *p*-cymene moiety in the **dia1/dia2** pair (Table S7 in SI). This is evidenced notably in the calculated Ru-S distances, at 2.31 Å (R = Ph) and 2.39 Å (R = *t*-Bu) in their respective optimized geometries.

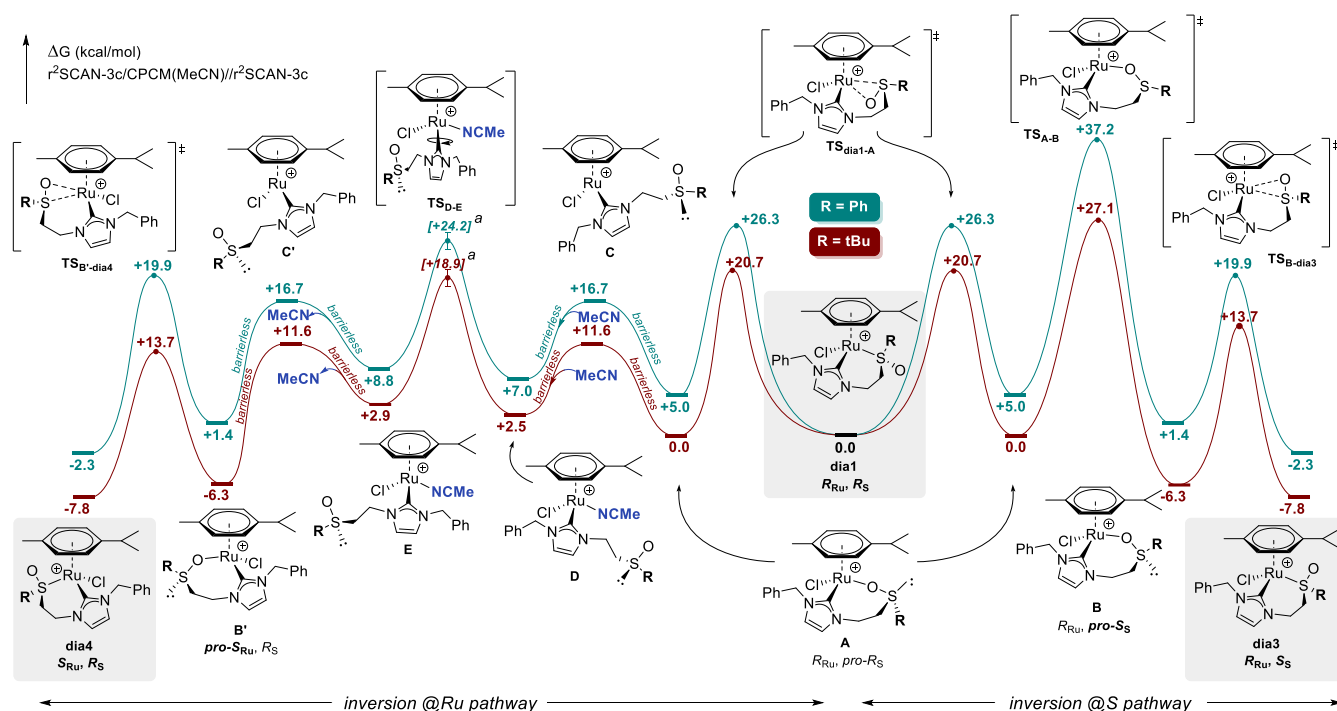


Figure 6. Computed free energy reaction profile for the interconversion between diastereomer dia1 to dia3 (via inversion of configuration at sulfoxide moiety, right) or to dia4 (via inversion of configuration at the Ru centre, left) for R = *t*-Bu (red) and R = Ph (green). ^a for the rotation step of the carbene moiety around the Ru–C axis, constrained conformational sampling was carried out along the scanned coordinate so as to avoid high energy artifacts stemming from resulting non-ideal conformations (See SI).

As direct inversion of configuration at the sulfoxide position whilst S-coordinated to the Ru centre is highly unlikely, we sought to exploit the possible hemilability of the sulfoxide moiety. The dissociation of the latter from **dia1** was found to occur via the O-bound congeners **A** with barriers of 20.7 kcal/mol and 26.3 kcal/mol for the *t*Bu and Ph analogues, respectively. Both are therefore accessible in the reaction conditions, and the change in coordination mode is even predicted to be isoenergetic in the *t*Bu case. This coordination mode allows for pyramidal inversion at the sulfur position, with an overall barrier of 27.1 kcal/mol for the *t*Bu congener and 37.2 kcal/mol for R = Ph (**TS_{A-B}**). The **dia3** topology is finally obtained by reverting to the S-coordination mode in a thermally accessible manner. While both inversion barriers were calculated to be lower than for the free ligands, likely through electron density depletion from the coordination to the cationic Ru centre (*vide infra*), it is apparent that only the *t*Bu system may be prone to inversion via this pathway in the reaction conditions (Table S8 & S9 in SI).

A second pathway was envisioned involving complete dissociation of the sulfoxide moiety to allow the inversion of configuration to happen at the Ru centre. From the previously calculated O-bound intermediate **A**, complete dissociation was found to be thermodynamically feasible, yielding (pseudo planar) intermediates **C** in a barrierless fashion. This intermediate is then readily stabilized by a solvent molecule to yield intermediates **D**, slightly uphill with respect to **dia1**. The relative energy of species along the path of free rotation around the Ru–C_{NHC} axis is highly conformation-dependent. That step was therefore investigated with conformational sampling along the rotation trajectory, which allowed an estimation for the rotation barrier at 18.9 kcal/mol and

24.2 kcal/mol for the *t*Bu and Ph systems respectively. Finally, dissociation of the solvent molecule was also found to be barrierless and allows the coordination of the sulfoxide moiety at the opposite face of the Ru centre through the oxide (**B'**). The following rearrangement to S-coordination finally yields **dia4**.

In summary, two pathways for interconversion between the diastereomer pairs were identified, with the inversion of configuration at the Ru, through rotation of the NHC moiety, featuring the lowest activation energy of the two. Of note, these calculations suggest that an enantiomerically pure sulfoxide moiety would yield an enantiomerically pure complex: upon reaching the lowest energy diastereomer, the barrier for pyramidal inversion at sulfur reaches 34.9 kcal/mol and 39.5 kcal/mol for R = *t*Bu and R = Ph, respectively.

The surprising and perhaps counter-intuitive inability of the Ph group to promote easier sulfoxide inversion compared to a *t*Bu group prompted us to look closer at the effect of electronics on the inversion barrier (Figure 7).

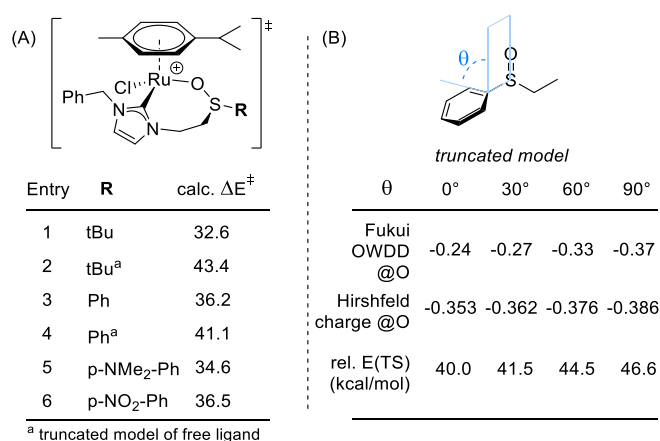


Figure 7. (A) Computed electronic energy barriers for the sulfoxide's pyramidal inversion with respect to the lowest O-bound intermediate and for the model, uncoordinated substrates at the r^2 SCAN-3c level; (B) Fukui orbital weighted dual descriptor (OWDD) and Hirshfeld partial charge at the oxygen position in the transition state geometries and associated inversion relative energy barriers, varying the Ph group's deviation from coplanarity with respect to the inversion plane.

Indeed, conjugation of the sulfoxide's lone pair into the aromatic system in the planar sp^2 transition state is expected to stabilize it and lower the overall inversion barrier. This is easily verified when comparing a *t*-Bu- and a Ph-substituted truncated model (Figure 7(A), entry 2 vs entry 4). The trend is completely reversed upon coordination to the Ru centre (entry 1 vs entry 3). Even more surprisingly, electron donating groups in *para* position help lower the barrier marginally (entry 5) while electron-withdrawing groups have the opposite effect (Table S11 in SI).

Closer examination of the geometries of the Ru-bound inversion transition states reveals that the aryl group's orientation with respect to the sulfoxide plane approaches orthogonality, preventing any delocalization, as opposed to the uncoordinated model system which adopts a fully planar topology. The computed atomic descriptors on the oxygen at the transition state geometry of the truncated model (Fukui OWDD and Hirshfeld partial charge) both show that increased deviation from planarity results in an accumulation of electronic density at the O, which is thought to result in a better binding interaction with the cationic Ru centre, through both electrostatics and orbital stabilization. Thus, electron density delocalization through coordination to Ru is sufficiently strong to completely offset the potential stabilization from aromatic conjugation, so that transition state geometries always show preference towards an orthogonal aryl group. This observation is also consistent with the lower computed barrier for the inductive donating *t*Bu congener.

VT-NMR experiments

Variable-temperature ^1H NMR studies of the compounds in CD_2Cl_2 between 298 and 193 K were carried out on the **4c** complex in order to observe possible dynamic processes (see SI, Figure S4-6). Decreasing the temperature (down to 198 K) did not give rise to any additional signals for the N/S methylene and *t*Bu protons. Only the de-coalescence of the *p*-cymene protons was observed, due to the slowing down of the rotation around the

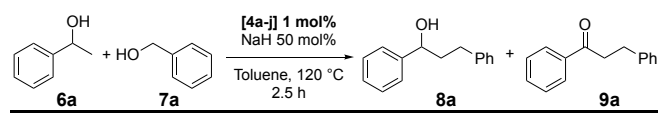
coordination axis of Ru.^[40] These results suggest that compound **4c** has a fixed stereochemical rearrangement without decoordination.

Catalysis

Recently, thioether functionalized NHC/Ru(cymene) piano stool complexes have been applied to several acceptorless dehydrogenation reactions.^[21, 23] More recently this catalytic system was successfully applied in the β -alkylation of primary alcohols and secondary alcohols by dehydrogenative coupling.^[21] We wondered whether a larger inversion barrier would lock in the dynamic processes of isomerization and conformational isomerism during sulfur coordination. This would better define the coordination sphere, and could be beneficial for the β -alkylation reaction.

The influence of the sulfoxide moiety was first evaluated using the optimal experimental conditions described for ruthenium NHC thioether complexes (as shown in Table 1).^[21] The reaction time was deliberately set at 2.5 h, before total conversion of the reagents, in order to better discern the parameters that may influence the selectivity and reactivity. High conversions were generally observed for alkyl sulfoxides for which complexes **4c** and **4d_{PF6}** (R = *t*-Bu and Ad) lead to the highest conversion, accompanied by high β -ol selectivity (Table 1 entries 3 & 4). The best selectivities with respect to the β -alcohol product were obtained with catalysts bearing aromatic groups **4f-j** (Table 1 entries 6-10). Nevertheless, complexes bearing a bulky electron-donating alkyl group on the sulfur atom provided a cleaner reaction mixture than the aryl counterparts, in which only the presence of the desired product **8a** was observed. The S-Ad complex **4d_{PF6}** was chosen for the remainder of this study, (Table 1, entry 4) where several bases, solvents and concentrations were tested.

The use of a slightly softer base (*t*BuOK), instead of NaH,^[21] was found to promote this reaction more efficiently (see SI; table S3). Due to the propensity of the sulfoxide to coordinate a second metal ion,^[41] the effect of the $[\text{tBuO}][\text{cation}]^+$ was investigated. Results show that the nature of the cation has a strong influence on selectivity, K^+ counterion being proven to be the best choice (96:4, see SI; table S3 entry 8).^[42] With the best available base, the nature of the solvent as well as the effect of concentration were also examined (Table S4 and S5), demonstrating that THF provided the optimum conditions, with high selectivity at full conversion (Table S4 entry 8). Large and weakly coordinating lipophilic anion such as tetrakis(3,5-bis(trifluoromethyl)phenyl)borate (BAR_F) has often a positive influence on the catalyst's efficiency.^[43] However, **4d_{BARF}** displayed lower activity (74%) than the corresponding **4d_{PF6}** (Table 1 entry 5).

Table 1. Evaluation of the β -alkylation of secondary alcohols using primary alcohols in presence of thioether-functionalized NHC-Ru complexes **4a-j**.^a


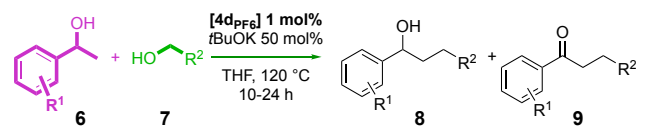
Entry 1 ^[a]	Ru	S-R ¹	Conv. % ^[b]	8a/9a ^[c]
1	4a	Et	94	88/12
2	4b	Cy	97	88/12
3	4c	<i>t</i> -Bu	99	89/11
4	4d_{PF6}	Ad	98	89/11
5	4d_{BARF}	Ad	74	92/8
6	4e	Ph	94	92/8
7	4f	<i>p</i> -Me-Ph	85	94/6
8	4g	<i>p</i> -OMe-Ph	96	92/8
9	4h	<i>p</i> -Br-Ph	89	94/6
10	4i	<i>p</i> -CF ₃ -Ph	94	93/7
11	4j	3,3'-CF ₃ -Ph	86	89/11

[a] 1-phenylethanol (0.5 mmol), benzyl alcohol (0.5 mmol), cat. (1 mol%), base (0.25 mmol), toluene (1 mL) at 120 °C, Ar, 2.5 h. [b] Conversion of 1-phenylethanol determined by ¹H NMR using hexadecane as internal reference and GC analysis (average of at least two runs). [c] Percentage of products were determined by ¹H NMR analysis.

Based on the above optimisation the substrates **6** and **7**, were reacted in the presence of the **4d_{PF6}** complex. Table 2 shows several combinations of primary **7a-f** and secondary alcohols **6g-j** for the formation of the alkylated products. The presence of an electron-withdrawing group such as -CF₃ (24h) significantly slows down the reaction and the use of long aliphatic chains (50h) further aggravates the situation to achieve complete conversion (table 2 entries **8d** and **8f**, respectively). Overall, substitution on the aromatic ring of the benzyl group in substrate **7**, drops the selectivity of the β -ol by about 11-17% (Table 2 **8b-e** vs. **8a**). Keeping **7a** constant, the reaction with several secondary alcohols (**6g-j**) was then investigated. In this case, the same reactivity was observed irrespective of the nature and position of the substituent. Although, the selectivity drops by the use of **6h** as reactant (table 2 entry **8h**). However, it should be noted that this catalytic system shows excellent tolerance towards sterically more hindered secondary alcohols such as **6g** and **6j** providing the desired product with very high β -alcohol selectivity 94/6 (table 2, **8g** and **8j**). This specificity is even more pronounced when 1-(*o*-tolyl)ethan-1-ol **6g** is used instead of unsubstituted 1-phenylethanol **6a**, which significantly improves β -selectivity (compare **8a/8g**; **8b/8k**; **8c/8l**; **8e/8m** and **8f/8n**).

Compared with other NHCs hybrid bidentate catalyst, NHC-SO (TOF = 2-10 h⁻¹) remains more active than NHC-Phosphine^[21b] (TOF = 1 h⁻¹) and NHC-pyrimidine^[21a] (TOF = 3 h⁻¹), but are slightly less active than NHC-SR^[21] (TOF = 17 h⁻¹), NHC-

picoly^[21e] (TOF = 23 h⁻¹), NHC-amido (TOF = 24 h⁻¹),^[21e] 1,2,4-triazole core with *N*-picolyl acetamido-furan wings^[3b] (TOF = 24 h⁻¹).^[44] However, though the NHC-SO **4d_{PF6}** catalyst shows good selectivities, it remains much less active than Rit's heteroditopic imidazole/triazole NHC-Ru catalyst (TOF = 16500 h⁻¹)^[21f] and Kundu's tridentate NHC-phenanthroline complex (TOF = 12000 h⁻¹).^[21c]

Table 2. Reaction scope of β -alkylation of secondary alcohols using primary alcohols in presence of thioether-functionalized NHC-Ru complexes **4d_{PF6}**.^[a]


8a : R = 78% (92:8) conv 100%, 10 h	8b : R = 60% (79:29) conv 100%, 18 h	8c : R = 80% (81:19) conv 100%, 17 h
8d : R = 50% (85:15) conv 100%, 24 h	8e : R = 62% (75:25) conv 100%, 14 h	8f : R = 51% (74:26) conv 100%, 50 h
8g : R = 84% (93:7) conv 100%, 14 h	8h : R = 45% (52:48) conv 100%, 14 h	8i : R = 80% (79:21) conv 100%, 24 h
8j : R = 60% (94:6) conv 100%, 24 h	8k : R = 59% (91:9) conv 100%, 16 h	8l : R = 48% (89:11) conv 100%, 20 h
8m : R = 83% (94:6) conv 100%, 19 h	8n : R = 39% (86:14) conv 100%, 69 h	

[a] secondary alcohol (0.5 mmol), primary alcohol (0.5 mmol), cat. (1 mol%), base (0.25 mmol), THF (0.2 mL) at 120 °C, Ar, 2.5 h. Yields refer to isolated yield after purification on column chromatography.^[45] Ratios (**8/9**) of products were determined by ¹H NMR and GC analyses. Conversion of 1-phenylethanol were determined by ¹H NMR using hexadecane as internal reference (average of at least three runs).

Conclusion

In summary, we have used a simple and straightforward oxidation protocol for the synthesis of new sulfoxide-functionalized NHCs from thioether-functionalized NHCs. The use of HFIP solvent allowed sulfone overoxidation to be completely suppressed, enabling NHC-sulfoxides to be obtained in very good yields. This method allows the Alkyl/Aryl group of the sulfinyl function to be easily modified. A new family of cationic Ruthenium (κ^2 -C,S)-[Ru^{II}(η^6 -*p*-cym)(NHC-SO)][X] (X = PF₆; BARF) complexes has been synthesized and well-characterized. The S-coordination mode of the sulfinyl group was secured by X-ray diffraction studies and, surprisingly, in the solid state, only one ruthenium diastereomer

was observed in the form of an enantiomeric pair instead of the expected diastereomeric mixture. The intrinsic energy differences between the two diastereoisomeric pairs and the calculated energy barriers are consistent with this diastereoselectivity. Stepwise hapticity change, sulfoxide decoordination and recoordination result in an effective inversion of configuration at Ru in a thermodynamically accessible manner from the least favourable diastereoisomers to provide the thermodynamic product. Access to the latter by pyramidal inversion of the sulfoxide is conversely less likely as it is associated with a higher energy barrier that can only be accessed for systems with a bulky sulfoxide moiety, from the high-energy diastereoisomer and in an irreversible manner. Among the different NHC-SO ligand structures, the ruthenium **4d_{PF6}** cationic complex was found to be the most active catalyst for the β -alkylation of the secondary alcohol. These ligands offer high reactivity but good to moderate selectivity, mainly due to the fact that the system is highly substrate dependent. Interestingly, high selectivity was achieved with our catalyst for sterically more demanding secondary alcohol substrates. In view of these results and this specificity, further studies aimed at improving the catalytic system are currently underway in our laboratory.

Supporting Information

General experimental procedures, additional schemes and figures, characterization data and NMR spectra associated with this work are available in the Supporting Information. Deposition Number(s) <https://www.ccdc.cam.ac.uk/services/structures?id=doi:10.1002/chem.202401390> (for **4b**), 2341795 (for **4c**), 2341796 (for **4d_{BARF}**), 2341798 (for **4e**) contain(s) the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe <http://www.ccdc.cam.ac.uk/structures> Access Structures service.

The authors have cited additional references within the Supporting Information.^[12a, d, 23a, 27, 29, 46-52]

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Conflict of Interests

The authors declare no conflict of interest.

Keywords: NHC ligands • Sulfoxide • diastereoselective • β -alkylation • ruthenium

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