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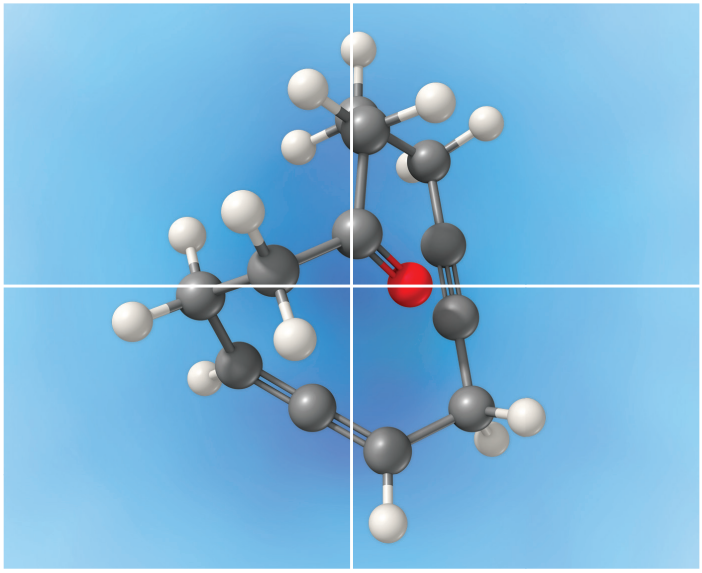

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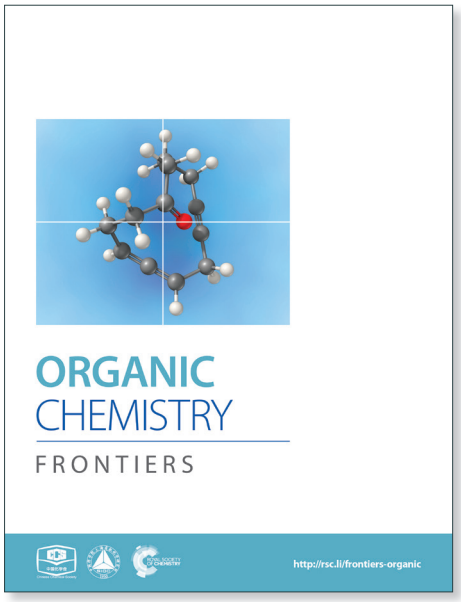

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ARTICLE

Cyclometallated Ruthenium(II) Complexes with ditopic Thienyl-NHC Ligands: Syntheses and Alkyne Annulations

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Dedicated to Professor F. Ekkehardt Hahn on the occasion of his 60th birthday

A series of six [RuX(2-thienyl-NHC)(*p*-cymene)] complexes (**9a-c** and **10-14**; X = halido) have been prepared via NHC directed C-H activation. All complexes have been fully characterized, and the molecular structures of four complexes are reported. The rotational barrier of the N-benzyl substituent in the bromido complex **9b** has been measured by variable temperature ^{1}H NMR spectroscopy. Preliminary reactivity studies of complex **12** with alkynes provided four new annulated aza-heterocyclic thiophenes.

Introduction

In the past decades, transition metal-mediated C-H functionalizations have emerged as powerful tools for the synthesis of valuable products from inexpensive starting materials.[1] Generally, the C-H activation is initiated by the binding of the transition metal to a directing group so that the adjacent C-H bond can be selectively activated to form metallacycles. The metallacycles then undergo subsequent reductive eliminations upon reaction with various substrates to produce the functionalized products.[1i,2]

Commonly, weak σ and π donors are selected as directing groups for the C-H functionalizations in order to facilitate the reductive elimination.[3] Catalytic C-H activation/alkyne annulations assisted by weaker donors have also been developed previously.[23] On the other hand, strong carbon donors, such as N-heterocyclic carbenes (NHCs), are seldom used as directing groups due to their innate strong donating abilities, which would make the respective C-M bonds more inert toward reductive eliminations.[4] As a result, only a few NHC-based metallacycles have been reported in a long period of time.[5] A few research groups reported examples of NHC-directed alkyne annulations assisted by stoichiometric or catalytic amount of ruthenium or rhodium complexes. Using this methodology functionalized azoles or azolium salts can be synthesized.[6,7]

Meanwhile, the interest in the C-H functionalizations of heterocycles (Het-H functionalization)[8] has increased tremendously as functionalized heterocycles have a plethora of applications in the fields of agrochemicals, functional materials and drugs.[9] Among these, annulated thiophenes incorporated into aza-heterocycles have demonstrated unique medicinal properties. For example, annulated thiophenes that bear benzimidazole moieties exhibit promising cytotoxity against cancer cells,[10] and have potential as DNA intercalators. Furthermore, these compounds could have potential optical applications due to their planar structure and enhanced chemical stabilities.[11] Therefore, it is desirable to explore new and facile synthetic approaches to annulated aza-heterocyclic thiophenes.

Herein, we report our preliminary study on the thiophene annulation through C-H bond functionalization. Several cyclometalated Ru-thienyl-NHC complexes (NHC = imy or bimy) were synthesized and characterized. Subsequently, four annulated aza-heterocyclic thiophenes (aza-heterocyclic = imidazolium or benzimidazolium) were easily obtained from the metallacycles via reductive eliminations on treatment with different alkynes.

Results and discussion

Synthesis of the ligand precursors. The ligand precursors **3**–**8** were obtained by a two-step sequence that is summarized in Scheme 1. The Cu(I) catalyzed Ullmann-type coupling of imidazole or benzimidazole with 2-bromothiophene in the present of L-proline afforded the mono-arylated compounds **1** and **2** in good yields (Scheme 1).[12] The copper salts generated as byproducts in this procedure can be easily separated from the organic products by a modified extractive work-up. Accordingly, these salts were converted into water-soluble copper-ammine complexes by addition of aqueous ammonia to the reaction mixture.[13]

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† Electronic supplementary information (ESI) available. Experimental procedures; characterization data; ^{1}H and ^{13}C{H} NMR spectra; Selected crystallographic data. CCDC 1424745 for **9a**, 1424802 for **9b**, 1424788 for **11** and 1424805 for **12**. For ESI and crystallographic data in CIF or other electronic format see:
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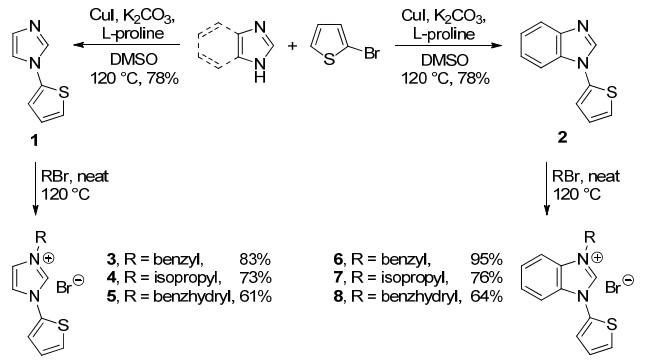
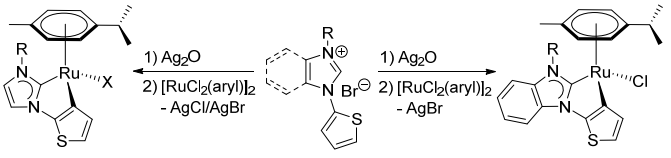
Subsequent N-alkylations of compounds **1** and **2** with excess alkyl bromides give rise to the functionalized precursor salts **3–8** in moderate to good yields (Scheme 2). All these compounds are soluble in chlorinated solvents such as dichloromethane and chloroform. The stepwise decrease in yields going from **3** to **5** can be explained by the increasing bulkiness of the alkylation reagent, and the same trend was observed for the yields of **6** to **8**, respectively.



Scheme 1. Two-step synthesis of ligand precursors **3–8**.

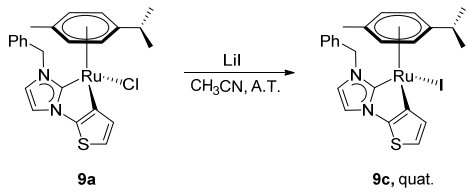
Synthesis and characterization of the Ru(II) NHC metallacycles. The preparation of complexes **9a, 9b** and **10–14** were carried out by treating the precursor salts **3–8** with Ag_2O and subsequent addition of $[Ru(p\text{-cymene})Cl_2]_2$ at ambient temperature (Scheme 2). The *in-situ* Het-H activation is anticipated to occur after the silver-carbene mediated ruthenation.[14] Since the formation constant for AgBr is larger than that for AgCl, the chlorido ligand is expected to be retained at the ruthenium centre, while the carbene transfer is expected to be driven by AgBr precipitation. Surprisingly, the reaction involving salt **3** yielded the bromido complex **9b** as the major product in 50% yield, while the expected chlorido complex **9a** was obtained in only 41% due to halide scrambling (*vide infra*). In order to complete the halido series, the iodido complex **9c** was also prepared in quantitative yield by a chlorido-iodido ligand exchange reaction by treating **9a** with excess lithium iodide (Scheme 3).



Scheme 2. Synthesis of ruthenium metallacycles **9a**, **10–14**.

In contrast, halide scrambling did not pose a problem in the complexation of salt **4** and **5** that bear more bulky N-substituents. Here, the chlorido complexes were formed predominantly, and only trace amounts of the bromido complexes were detected. A similar observation was made for benzimidazolium salts **6–8,** where the chlorido products **12–14** were obtained as major products regardless of the N-substituents.

Complexes **9**-**14** were isolated in moderate to good yields as microcrystalline, yellow solids, which are readily soluble in most organic solvents such as MeOH, DMSO, DMF and CH_3CN, but insoluble in nonpolar solvents, such as hexane, diethyl ether and toluene. They are stable for months in solutions under aerobic conditions at ambient temperature. However, these complexes were found to slowly decompose during purification attempts of the crude products by column chromatography on silica gel. Furthermore, when pure samples of the complexes were dissolved in unstabilized, deuterated chloroform, a color change of the respective solutions from yellow to green was observed after several hours. Both observations indicate the sensitivity of these complexes towards slightly acidic materials, where easy acidolysis of the Ru-C_{thio} bonds can be anticipated.[2b,15] To circumvent this process, all the crude complexes were subsequently purified using neutral alumina, and all the NMR samples were prepared by using $CDCl_3$ that was passed through a short pad of alumina to remove traces of hydrochloric acid.



Scheme 3. Synthesis of iodido complex **9c**.

The formation of complexes **9–14** was confirmed by multinuclear NMR spectroscopies and mass spectrometry. In the ^1H NMR spectra, the absence of downfield signals characteristic for the azolium salts and the presence of resonances for both the N-substituents and the bimy/imi ligands indicated the formation of the expected complexes. In each complex, the loss of symmetry upon cyclometalation results in the diastereotopy of the *p*-cymene protons, which resonate as four doublets ranging from 6.0 to 5.0 ppm with a geminal coupling constant of around $^2J(H,H)$ = 6 Hz.

The two benzylic protons in the chlorido complex **9a** give rise to a singlet at 5.73 ppm in the ^1H NMR spectrum. In contrast, the respective spectra of the bromido and iodido complexes **9b** and **9c**, respectively, show two sets of doublets with resonances at 5.74 and 5.67 ppm (for **9b**) or 5.73 and 5.68 ppm (for **9c**), respectively, with geminal coupling constants of $^2J(H,H)$ = 17 Hz indicative of diastereotopic benzylic protons.

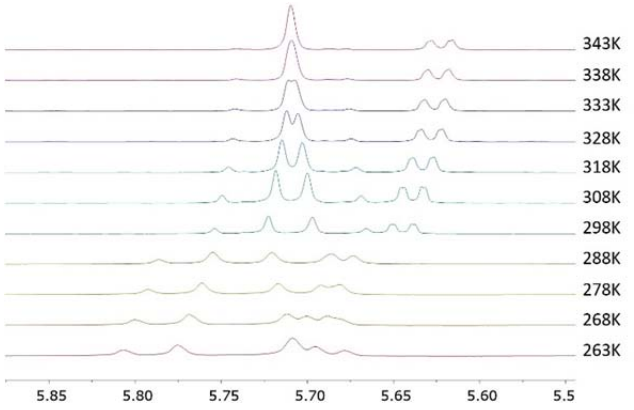
This observation supports the view that the rotational freedom of the N-benzyl substituent is largely affected by the nature of the halido ligands. In complex **9a**, the rotational barrier is anticipated to be low due to the presence of the smaller chlorido ligand. The successive replacement of the latter by

the larger bromido and iodido ligands leads to an increasingly difficult rotation around the N–CH_2 single bond in complexes **9b** and **9c**, respectively, as a result of steric crowding around the metal center. This in turn is manifested in the diastereotopic splitting of the initial singlet observed for **9a** into two doublets in the spectra of **9b/c** each with half integral values.

To get more insights into the relative rotational barriers for complexes **9a–c**, a series of variable temperature (VT) ^{1}H NMR experiments were carried out in $CDCl_3$. Even at a low temperature of 233 K, fast exchange between the two benzylic protons was still observed for the chlorido complex **9a**, indicating that the activation energy for the rotation for the benzyl group in **9a** is very low.[16] Another VT ^{1}H NMR study was carried out for the bromido complex **9b** (Fig. 1). Here, a minimal proton exchange was noted at 268 K with a maximum chemical shift separation of Δv = 45 Hz. Upon slow warming of the sample, the initial separate signals start to merge at ~328 K, and coalescence for the diastereotopic benzylic protons occurs at ~343 K allowing for an estimation of the rotational barrier as 16.9 kcal/mol.[17] In contrast, the benzylic proton signals for iodido complex **9c** did not coalesce in this temperature range, providing evidence that proton exchange in this case is much slower even at higher temperatures.[16] Thus, a higher rotational barrier is to be expected for **9c**.

In the ^{13}C NMR spectra for complexes **9a–14**, the carbene signals resonate at 188.9, 188.4, 188.3, 186.5, 189.6, 202.6, 200.8 and 203.3 ppm, respectively. These chemical shifts are notably more downfield compared to $^{13}C_{carbene}$ signals of related [$RuCl_2$(η^6-*p*-cymene)(NHC)] analogues, which are not cyclometalated.[18] The formal replacement of a chlorido ligand by a supposedly stronger anionic carbon donor results in a less Lewis acidic ruthenium centre leading to an expected downfield shift of the carbene carbon.[19] Moreover, the carbon donors of thienyl moiety of complexes **9a–14** were identified at 155.7, 154.8, 154.9, 155.2, 155.7, 153.7, 154.3 and 154.6 ppm, respectively, by means of the 2D NMR spectroscopy.

Figure 1 Section of the Variable-temperature ^{1}H NMR spectral plot of complex **9b** in $CDCl_3$



Molecular structures. X-ray diffraction analyses were carried out on single crystals of **9a**, **9b**, **11** and **12**, which were obtained by slow diffusion of diethyl ether into their concentrated solutions in dichloromethane (Fig. 1). Although all complexes are chiral-at-metal, they expectedly crystalized in racemic forms due to the lack of chiral induction from the achiral ligands.

Figure 2. Molecular structures of **9a**, **9b**, **11** and **12** showing 50% probability ellipsoids. Solvent molecules and hydrogen atoms are omitted for clarity.

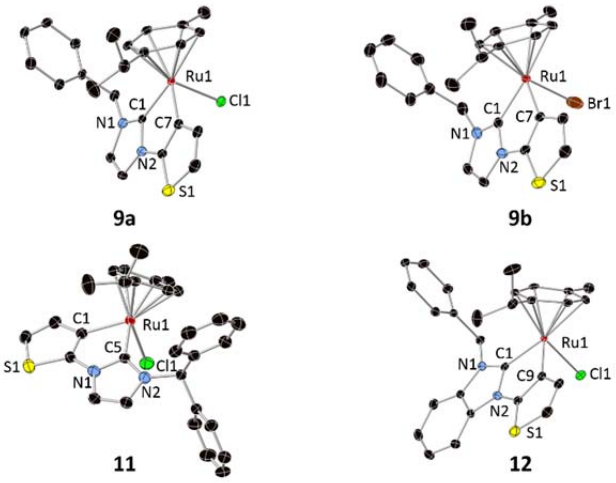


Table 1. Bond distances (Å) and angles (deg) in complexes **9a**, **9b**, **11** and **12**

Bond parameter	9a	9b	11	12
Ru-C_{thio}	2.0660(16)	2.0646(19)	2.0555(19)	2.0575(19)
Ru-$C_{carbene}$	2.0460(15)	2.047(2)	2.0353(18)	2.024(2)
Ru-halide	2.4301(4)	2.493(10)	2.4260(8)	2.4203(7)
Halide-Ru-C_{thio}	87.52(4)	86.23(6)	90.11(5)	87.45(6)
Halide-Ru-$C_{carbene}$	87.22(4)	86.12(6)	84.23(5)	87.50(5)
C_{thio}-Ru-$C_{carbene}$	77.30(6)	77.07(8)	76.79(7)	77.49(8)
Ru-Ct	1.7181(2)	1.7265(2)	1.7237(3)	1.7317(5)

Ct denotes centroid of the *p*-cymene ring.

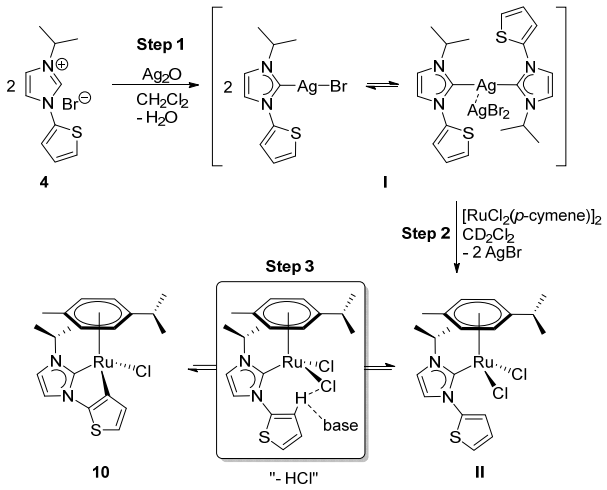
In each of the molecular structures, the Ru atom lies in a pseudo-octahedral environment. The half sandwich complexes adopt a piano-stool configuration with the *p*-cymene ligand as the "stool" and the "tripod" is composed of the chlorido, NHC and thienyl donors. The N-substituents point away from the *p*-cymene ligand in order to circumvent steric repulsion. Cyclometalation leads to formation of planar tricyclic (imy) or tetracyclic (bimy) metallacycles incorporating both NHC and thienyl rings in each of the structures. The dihedral angles defined by the metallacycles and the *p*-cymene planes are 55.3° (α_1) for **9a**, 55.8° (α_2) for **9b**, 50.9° (α_3) for **11** and 55.5° (α_4) for **12**, respectively. The α_3 angle of **11** is significantly smaller than α_1 of **9a**, indicating the greatest repulsion between the more bulky N-benzhydryl substituent and the *p*-cymene ligand in **11**, which forces the metallacyclic plane closer to the *p*-cymene ligand. On the other hand, α_1 and α_2 are comparable despite the presence of different halido ligands in complexes **9a** and **9b**. Although the halido ligands have a great influence on the rotation of the N-benzyl group

(*vide supra*), their impact on the *p*-cymene is expectedly minimal as they point away from the aryl ligand. Similarly, benzannulation of the NHC ring does not result in any significant distinction between the α_1 and α_4 angles in **9a** and **12**, respectively.

Selected bond lengths and angles are listed in Table 1. The Ru-C_{thio} bond lengths fall in the range of 2.0555–2.0646 Å. These values do not deviate significantly from other Ru complexes bearing cyclometalated thienyl moieties.[20] The Ru–$C_{carbene}$ bond lengths for complexes **9a** and **9b** averaging to 2.046 Å are identical within 3σ. However, these bonds for complexes **11** (2.0353(18) Å) and **12** (2.024(2) Å) are slightly shorter, making their ruthenium centers sterically more congested.

The ruthenium-centroid (Ru-Ct) distances also reflect the stereoelectronic properties of the respective ligands. The replacement of the chlorido (**9a**) with a bromido ligand (**9b**) leads to elongation of this bond parameter, which is consistent with the greater spatial demand of the larger bromido ligand. Similarly, substitution of the N-benzyl (**9a**) with the bulkier benzhydryl wing-tip (**11**) also results in a longer ruthenium-centroid distance. However, the most significant difference occurs upon benzannulation of the NHC ligand. Here, electronic factors are at play, since complexes **9a** and **12** are sterically very similar. The imidazolin-2-ylidene ligand in **9a** is more strongly donating and enhances backdonation from the metal to the *p*-cymene ligand, which in turn results in a shorter Ru-Ct separation.

Proposed mechanism of C-H activation. The ease of C-H activation that did not require addition of excessive external base in our one-pot protocol was surprising and called for a more detailed investigation. Thus, ^{1}H NMR tracing of the C-H activation step was attempted (see ESI). For this purpose, salt **4** was chosen due to its simpler NMR spectroscopic signature, and it was reacted with silver(I) oxide in a 2:1 ratio to form the respective silver-NHC complex **I** (Scheme 4, Step 1). The compound was isolated as a white powder, and characterized by ^{1}H NMR spectroscopy. Subsequently, a mixture of the pre-isolated silver-species and half-equivalent of the Ru-dimer was taken up in CD_2Cl_2 in a NMR tube for monitoring (Step 2). Fast transmetallation to ruthenium was indicated by an immediate precipitation of silver halide. More important, resonances due to the silver-carbene and the ruthenium dimer decreased significantly, and signals including a multiplet at 2.74 ppm, a singlet at 2.00 ppm and two doublets at 1.50 and 1.23 ppm, of a new species bearing both cymene and NHC ligands emerged at ~10 min into the reaction (Fig. S5). We assign this to the formation of the neutral dichlorido-Ru^{II} complex **II** as a major product. In addition, small amounts of the final product **10** can be observed as evidenced by two low intensity doublets at 0.91 and 0.77 ppm, respectively. However, the ratios of the compounds did not change significantly even after 4 h (Fig. S6 and S7). Since no external base was added at this stage, one may suppose that the complex **II** and **10** are in a dynamic equilibrium, which lies predominantly on the side of the dichlorido species **II** (Step 3). In principle, the chlorido ligands could assist in the deprotonation of the thiophene moiety. However, this process is less favourable in an aprotic media, i.e. CD_2Cl_2. The addition of 1 equiv of silver(I) oxide led to an enhancement of the C-H activation process and after 3 h a compelling increase in the amount of **10** was detected (Fig. S8). After 7 h, the resonances from intermediate **II** have almost disappeared, while signals of complex **10** have become predominant (Fig. S9). In addition, a set of new signals attributed to free *p*-cymene appeared at 2.89 ppm (septet), 2.04 ppm (singlet) and 1.25 ppm (doublet) indicating partial decomposition upon prolonged standing in solution.



Scheme 4. Proposed mechanism of cyclometalation.

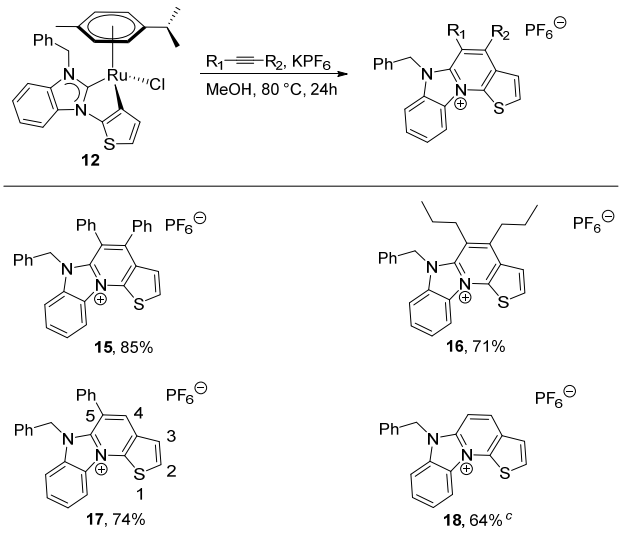
Overall, these observations are in line with the proposal that the C-H activation step is rate-determining and occurs likely base-assisted (e.g. CMD mechanism) as suggested in previous work.[23] Moreover, protic media (water is present in the one-pot procedure) and addition of external base facilitates this step and drives the formation of the cyclometalated species.

Synthesis of aza–heterocyclic thiophenes. In a preliminary study, N-benzylbenzimidazolin-2-ylidene complex **12** was chosen to test its reactivity with alkynes. In boiling methanol, it smoothly reacted with excess of different alkynes in the presence of excess KPF_6 to give the cationic aza–heterocyclic thiophenes **15–18**. Reaction of **12** with symmetrical and internal diaryl and dialkyl acetylenes generated **15** and **16** in good yields. For terminal alkynes, two possible isomers can be expected. Notably, a regiospecific annulation took place between **12** and the phenylacetylene, resulting solely in the 5–phenyl product **17** in 75% yield (*vide infra*).[21]

Finally, the 4,5-unsubstituted product **18** was generated in 64% yield from **12** and trimethylsilyl acetylene, which can be conveniently used in place of gaseous acetylene. In this case, a useful *in-situ* desilylation reaction occurs, which mechanism is currently unclear, but will be subject to future studies. The proposed reaction pathway for the formation of the aza–heterocyclic thiophenes is similar to that reported by the groups of Pfeffer,[22] Urriolabeitia[20d] and Ackermann[23] (Scheme 5), according to which the reaction is initiated by alkyne insertion into κ^2-*C,C* bound ditopic thienyl-NHC ligand. This is followed by an intramolecular, reductive elimination step,

which supposedly generates the intermediate ruthenium(0) adduct **IV** containing the new heterocycle. The latter is particularly short-lived and quickly collapses under liberation of the new aza-heterocyclic thiophene cation.

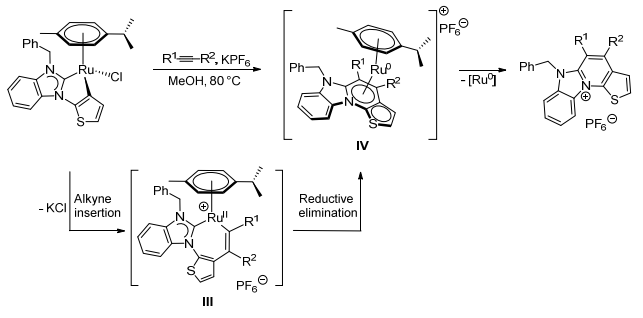
Table 2. Aza–heterocyclic thiophenes via alkyne annulation of complex **12** [a,b]



Reactions and conditions: [a]**12** (0.2 mmol, 1 eq), alkyne (0.5 mmol, 2.5 eq.), KPF_6 (1 mmol, 5 eq.), MeOH (3 mL), 80 °C, 24 h. [b]Isolated yields are given for an average of two runs. [c]Trimethylsilyl acetylene (0.5 mmol, 2.5 eq.) was used.

The intermediacy of ruthenium(0) species can be supported by the observed slow precipitation of ruthenium black during the course of the reaction. Moreover, it should be noted, that complexes reminiscent of **II**, but derived from cyclometalated N- and O-donors, have been structurally characterized by the aforementioned groups.[20d,22,23a] In the migratory insertion step of phenylacetylene, the alkyne tends to bind to the ruthenium(II) centre at the more substituted position (*i.e.* R^1 = Ph and R^2 = H). This generates a more stable intermediate **III** containing a sterically better protected metal centre, which eventually results in the regioselectivity observed in the synthesis of **17**.

Scheme 5. Proposed pathway for the formation of aza-heterocyclic thiophenes.



Conclusions

The NHC directed Het–H activation of the thienyl moiety has allowed for a rapid synthesis of Ru^{II}-thienyl-NHC metallacycles **9a–14**. All complexes are the first examples of cycloruthenated NHC complexes incorporating thienyl moieties and have been fully characterized. The C-H activation of the thienyl substituent is rate determining and occurs base-assisted and favourably in protic media. The rotational barrier of the N-benzyl substituent in complexes **9a-c** is halido dependent, and has been determined for the bromido complex **9b** by VT ^{1}H NMR spectroscopy. Moreover, alkyne annulations of complex **12** afforded four new annulated aza-heterocyclic thiophenes, which could have potential medical and optical applications. Work is in progress to further extend the substrate scope of the annulation reactions, to provide a more detailed mechanistic understanding and to explore catalytic variations of this reaction.

Acknowledgements

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