Communication

Dual role of Rh(III)-catalyst enables regioselective halogenation of (electron-rich) heterocycles

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J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.5b00283 • Publication Date (Web): 15 Jan 2015

Dual role of Rh(III)-catalyst enables regioselective halogenation of (electron-rich) heterocycles

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Supporting Information Placeholder

ABSTRACT: The Rh(III)-catalyzed selective bromination and iodination of electron-rich heterocycles is reported. Kinetic investigations show that rhodium plays a dual role in the bromination: i) catalyzing the directed halogenation and ii) preventing the inherent halogenation of these substrates. As a result, this method gives highly selective access to valuable halogenated heterocycles with complementary regiochemistry to those obtained using uncatalyzed approaches, which rely on the inherent reactivity of these classes of substrates. Furans, thiophenes, benzothiophenes, pyrazoles, quinolones and chromones can be applied.

Aromatic heterocycles are undoubtedly one of the most important structural motifs in chemical synthesis.[1] A major class of building blocks for the synthesis of heterocycles are halogenated compounds due to the versatility of the C-X group in a large variety of functionalization reactions,[2] especially cross couplings.[3] While most heterocycles can be selectively halogenated at a well-defined position due to their inherent selectivity resulting from the electronic properties of the compound, the direct halogenation to yield other isomers is often challenging and requires harsh reaction conditions and/or many synthetic steps. One prominent strategy is the directed *ortho* metallation (DoM), followed by a halogen quench.[4]

Directed transition metal-catalyzed C–H halogenation has emerged as a powerful tool for the complementary synthesis of halogenated building blocks.[5] Within the last few years a plethora of reports on the halogenation of benzene derivatives have been described, highlighting the importance of this transformation. The most often used metal for this transformation is palladium,[6] however other metals have also been applied.[7] To the best of our knowledge, only the group of Yu et al. has reported a transition metal-catalyzed C–H halogenation of aromatic heterocycles using a palladium catalyst and molecular I_2 as the oxidant.[6r] In this excellent report pyrazoles, oxazoles, thiazoles and pyridines could be used as suitable substrates. However, no directed halogenation for the synthesis of electron-rich heterocycles such as furans and thiophenes exists, which can override the inherent reactivity for these substrates (Figure 1).[8]

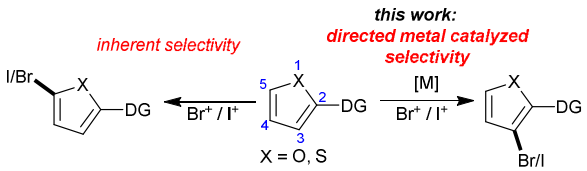
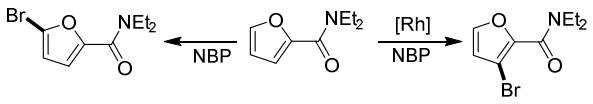


Figure 1. Switch of selectivity.

Encouraged by previous Rh(III)-catalyzed halogenations of arenes and alkenes,[9,10] we started our study using *N*,*N*-diisopropylfuran-2-carboxamide (**1**) as the standard substrate. Using 5 mol% of $[RhCp^*(MeCN)_3](SbF_6)_2$, *N*-bromosuccinimide (NBS) as the halogen source, pivalic acid as an additive and 1,2-DCE as the solvent, we were able to get the desired product already in a yield of 84% (see SI for further information), although in a mixture with 8% of the dibrominated product. Screening of different electrophilic brominating agents showed that the yield could be increased to an excellent 95% with *N*-bromo-phthalimide (NBP) instead of *N*-bromosuccinimide, while other reagents proved to be less effective. Remarkably, unlike most other Rh(III)-catalyzed C–H activations, no carboxylic acid or carboxylate was required to obtain high yields.[11] Notably the reaction works efficiently under air and no precaution needs to be taken to exclude moisture from the glassware.

Gratifyingly, the more useful *N*,*N*-diethylamide **2** also works effectively. Comparative reactions with **2** strikingly revealed that in both reactions excellent selectivity for the 3- or the 5-position was observed and no other isomers were detected by GC-MS analysis (Scheme 1).

Scheme 1: Regioselectivity in the rhodium catalyzed halogenation compared to the standard reactivity.



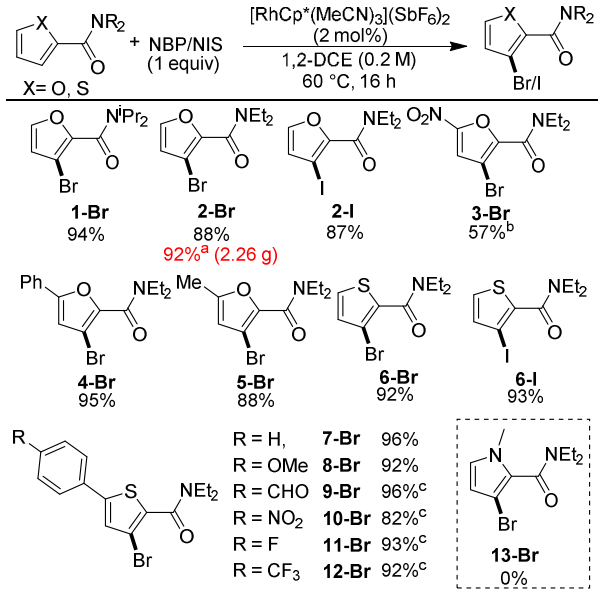
2-Br' 75% | **2** *>20:1 regioselectivity in both reactions* | **2-Br** 88%

Reaction conditions: 0.4 mmol scale in 1,2-DCE (0.2 M), 1 equiv of **1** and 1 equiv of NBP. 2 mol% $[RhCp^*(MeCN)_3](SbF_6)_2$ for the catalyzed reaction. Isolated yields are reported.

With the optimized conditions in hand, we examined the scope of different heterocycles with different substitution patterns, bearing the directing group in the 2-position (Table 1). For all substrates a control reaction omitting the catalyst was performed (see SI for the results). With *N*,*N*-diethylamide **2-Br** could be isolated in a very good yield of 88%, iodination with *N*-iodosuccinimide (NIS) gave a comparable yield of 87% (**2-I**).[12] In addition, a larger scale reaction (*10 mmol scale*) could be successfully run. With electron-withdrawing groups attached to the furan the reactivity decreased significantly and higher temperatures were needed to provide compound **3-Br** in an acceptable yield of 57%. Methyl and phenyl substituents were readily tolerated and the yield of the products were 88% for **5-Br** and 95% for **4-Br**. Product **5-Br** is a good example for the efficiency of the Rh(III)-catalyzed reaction, suppressing two different side reactions which

were found in the control reaction without any catalyst: the bromination in the 4-position occurred in 14% isolated yield, resulting most likely from an electrophilic pathway, and the bromination of the methyl-group occurred in 69% isolated yield, resulting from a radical reaction under the uncatalyzed conditions. Switching from furan to thiophene derivatives resulted in the same reactivity and excellent yields could be obtained. Several interesting functional groups (methoxy, aldehyde, nitro, trifluoromethyl, fluoro) were also well tolerated.[13] However, the very electron-rich pyrrole motif (**13**) could not be selectively halogenated under our reaction conditions. In this case the inherent reactivity predominated and the main product was the 5-halogenated derivative.

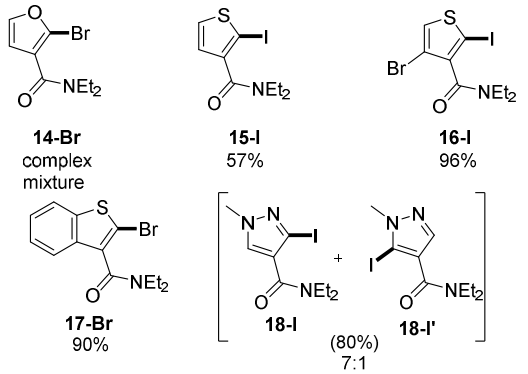
Table 1. Scope of the halogenation of furans and thiophenes with the directing group in the 2-position



All reactions were performed on a 0.4 mmol scale under air. Isolated yields are reported. [a] Reaction was performed on a 10 mmol scale. [b] Reaction temperature was 100 °C and 1.2 equiv. NBP were used. [c] Reaction was performed on a 0.2 mmol scale.

Unfortunately, *N*,*N*-diethylfurane-3-carboxamide **14** was not a suitable substrate for our catalytic system (Table 2). With and without the rhodium-catalyst, a mixture of the 2-brominated and 2,5-dibrominated product was observed in a complex reaction mixture.

Table 2. Scope of the halogenation of different heterocycles with the directing group in the 3- or 4-position.

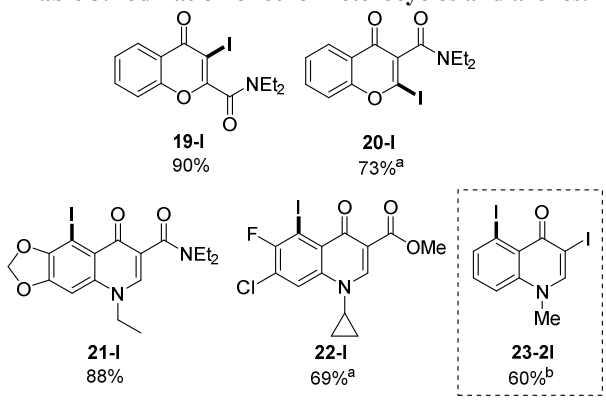


Reactions were performed on a 0.4 mmol scale under air, isolated yields are given. Conditions: $[RhCp^*(MeCN)_3](SbF_6)_2$ (2 mol%), NBP/NIS (1 equiv), 1,2 DCE (0.2 M).

In comparison to furans with the amide moiety in the 3-position, thiophenes such as **15** and **16** could be iodinated in moderate to excellent yields. In addition benzothiophene **17** also yielded the desired product **17-Br** in a very good yield of 90%. Applying the pyrazole **18** to the iodination conditions led to both possible regioisomers in a 7:1 mixture in a combined yield of 80%.

Additionally other important benzannulated heterocycles were tested under our reaction conditions (Table 3).[14] Chromones **19** and **20** and the amide derivative of oxolinic acid **21**, an antibiotic of the quinolone class, underwent iodination in good yields. Interestingly in the quinolone examples, iodination occurred at the 5-position rather than at the 2-position. This is most likely due to the steric demand of the nitrogen substituent, blocking the 2-position, as well as activation of the ring ketone group as a directing group through the nitrogen, which could be viewed as a vinylogous amide. In addition to amides ester **22** (the free acid is a precursor of Ciprofloxaxin, another quinolone type antibiotic) also underwent iodination, albeit only in a lower yield of 69%. To prove that the directing group is the vinylogous amide and the amide or ester function is not of importance, the quinolone core **23** was subjected to the reaction conditions. First we observed iodination of the 3-position, which is uncatalyzed due to the high reactivity of the enamine. Applying this mono-iodinated species to our reaction conditions led to a selective metal-catalyzed iodination of the 5-position.

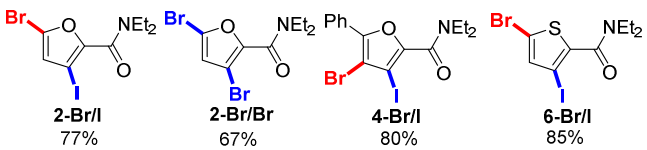
Table 3. Iodination of other heterocycles and arenes.



All reaction were performed on a 0.4 mmol scale. Reaction conditions: $[RhCp^*(MeCN)_3](SbF_6)_2$ (2 mol%), NBP/NIS (1 equiv), 1,2-DCE (0.2 M).[a] Reaction temperature was 100 °C. [b] 5 mol-% $[RhCp^*(MeCN)_3](SbF_6)_2$.

Due to the complementary reactivity of the metal-catalyzed and uncatalyzed halogenation we decided to see if these methods could be combined in a one-pot approach to synthesize highly functionalized heterocyclic building blocks (Scheme 2).[15] The yields for this one-pot procedure were generally very good; only for product **2-Br/Br**, where 2 brominations occurred, was a modest yield of 67% observed. Due to the presence of the rhodium-catalyst in this procedure, the second halogenation usually required longer reaction times (see also Figure 2). A key feature is,

Scheme 2. One-Pot Synthesis of multi-halogenated products.



One pot procedure: **1)** Rh-catalyst + NIS/NBP for complete 3-halogenation.
2) After full conversion another equivalent of NBP.

that for substrates with a blocked 5-position even the 3,4-dihalogenation occured in good yield. Thus this method allows the synthesis of the completely substituted furan **4-Br/I**.

To get a better understanding for the origin of the high levels of regioselectivity in the rhodium-catalyzed bromination of furan and thiophene, a kinetic study of the inherent bromination of the 3-bromo-substituted compound **2-Br**, both in the absence and in the presence of the rhodium-catalyst, was conducted (Figure 2).

The inherent, uncatalyzed bromination at the 5-position in the absence of rhodium showed an induction period, suggesting that the substrate does not directly react with NBP (The same effect was observed with thiophene **6-I**, see SI). We propose that the reaction partner is in fact Br_2, and that an initial reaction between NBP and HBr (or Br^-), formed under the reaction conditions, generates the active halogenating reagent. In the presence of the rhodium-catalyst, the rate of the inherent bromination at the 5-position is dramatically decreased. Presumably the rhodium complex acts as a bromide acceptor, retarding the formation of Br_2. This hypothesis is supported by the fact that $AgSbF_6$ also suppresses the uncatalyzed reaction while the addition of HBr accelerates the reaction (see SI for further kinetic studies). In addition we were able to isolate the $[RhCp^*Br_2]_2$-complex upon heating the cationic catalyst $[RhCp^*(MeCN)_3](SbF_6)_2$ with HBr. These results suggest that for substrates with free sites at both the 3- and the 5-position available for halogenation, the rhodium-catalyst plays two roles in ensuring high levels of regioselectivity. On one hand, rhodium catalyzes the directed halogenation at the 3-position with NBP as the bromine source while, on the other hand, suppressing the inherent reaction at the 5-position by retarding the formation of Br_2.

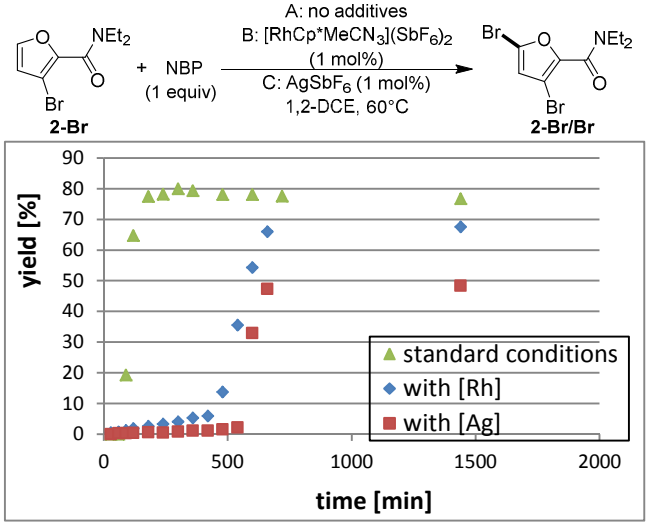
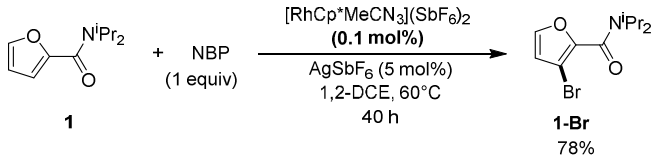


Figure 2: Inherent reactivity in the absence and in the presence of $[RhCp^*(MeCN)_3](SbF_6)_2$. Yield determined by GC-analysis.

We thought that the complexation of bromide by the rhodium-catalyst is also the major decomposition pathway of the active catalyst in our standard reaction. To prevent this pathway, we performed the bromination of **1** in the presence of 5 mol% $AgSbF_6$ as an additive to remove the bromide. Indeed, it was possible to perform the reaction with only 0.1 mol% catalyst, resulting in an excellent *turnover-number* of 780 (Scheme 3).

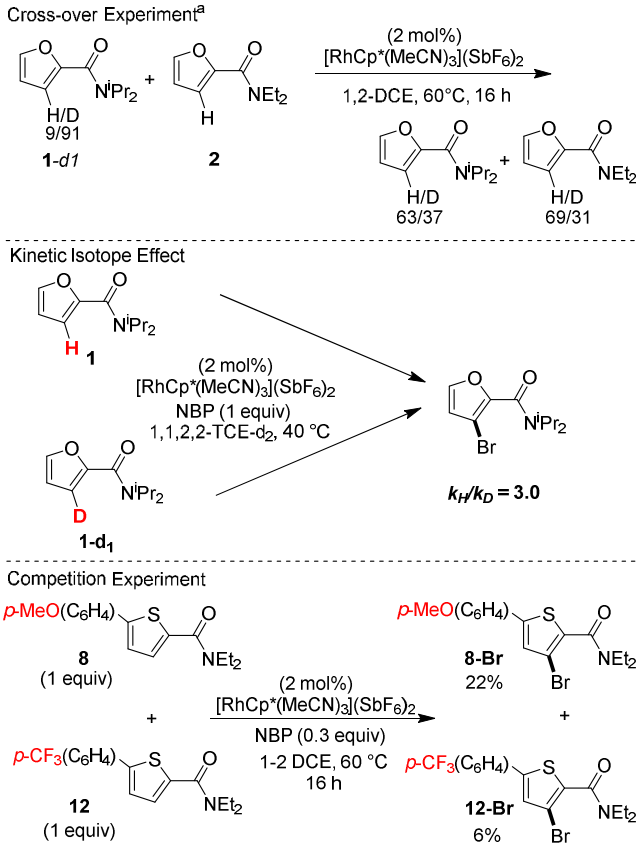
To gain some mechanistic insight into this transformation different experiments have been performed (Scheme 4). To elucidate the nature of the C–H-activation step, a cross-over experiment between deuterium enriched diisopropylamide **1**-d1 and diethylamide **2** was conducted. In the presence of 2 mol% of the rhodium-catalyst and no other additives, significant deuterium scrambling

Scheme 3: Bromination of 1 in the presence of $AgSbF_6$.



could be observed, indicating that no external base (i.e. the phthalimide) is needed for the C–H-activation step. A similar result was observed when using MeOD as an external deuterium-source (see SI).

Scheme 4. Mechanistic Experiments.



[a]0.20 mmol **2** and 0.17 mmol **1**-d1 were used. Deuterium distribution was analyzed by ESI.

A significant kinetic isotope effect was observed when measuring the rate constants of the reaction of **1** and **1-d$_1$**, indicating that the C–H activation step is turnover-limiting. A competition experiment between thiophene-substrates **8** and **12** showed that electron-poor substrates react significantly slower. While the absence of any carboxylate base and the preference for electron-rich substrates speak in favor of an electrophilic aromatic substitution pathway (EAS), the observance of a large kinetic isotope effect argues against this pathway.[16] A concerted-metallation-deprotonation (CMD) pathway may take place with the amide moiety of the substrate acting as a base. However, at this point, neither of the two mechanisms (CMD vs. EAS) can be ruled out.

Following the C–H activation event, two alternative scenarios seem plausible:

A) oxidation of the Rh(III)-intermediate with the halogenating agent to generate a Rh(V)-species, which releases the desired product after reductive elimination, and

B) direct nucleophilic attack of the rhodacycle at the halogenating agent to deliver the desired product.

In conclusion, a new method for the effective bromination and iodination of different classes of electron-rich heterocyclic compounds has been described. Key to success is a Rh(III)-catalyst that not only catalyzes the desired transformation, but also suppresses the inherent halogenation at the 5-position. It is likely that a similar behavior is also operative in other catalytic transformations. In addition, the benzannulated six membered heterocycles chromones and quinolones were also successfully iodinated.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic data, mechanistic experiments (KIE, competition, deuteration, kinetics). This material is available free of charge via the Internet at http://pubs.acs.org.

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ACKNOWLEDGMENT

We dedicate this manuscript to Prof. Günter Haufe (WWU) on the occasion of his 65th birthday. We thank Daniel Paul for assistance with the NMR experiments, Christian Vosse for experimental support and Tobias Gensch, Da-Gang Yu and Matthew Hopkinson for helpful discussions. Generous financial support by the DFG (IRTG Münster-Nagoya), the European Research Council under the European Community's Seventh Framework Program (FP7 2007-2013)/ERC Grant agreement no 25936 and the Alfried Krupp von Bohlen und Halbach Foundation (Alfried Krupp Prize for Young University Teachers) is gratefully acknowledged.

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(11) It has to be noted that NaOAc suppresses the reaction, while HOAc or $Cu(OAc)_2$ have no influence on the reactivity. Propably this is due to the fact that many free OAc anions coordinate to the Rh and therefore diminish its reactivity.

(12) In contrast to the bromination, the iodination was much slower the in absence of the rhodium-catalyst. NIS, which is commercially available in contrast to *N*-iodophthalimide (NIP) showed a similar reactivity to NBP and, thus, was used as reagent of choice for iodinations.

(13) For a more detailed robustness screen, see SI and: (a) Collins, K. D.; Glorius, F. *Nat. Chem.* **2013**, *5*, 597. (b) Collins, K. D.; Glorius, F. *Tetrahedron* **2013**, *69*, 7817.

(14) In most cases the iodination was shown to be more effective. The bromination with NBP often led to only lower conversions to the desired product.

(15) The rhodium catalyzed reaction was performed first, because the reaction is cleaner than the non-metal catalyzed one. If the order was changed, formation of side products and catalyst poisoning occured.

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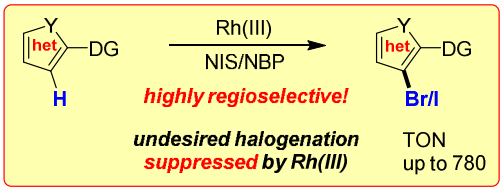
Y
het
DG
H
Rh(III)
NIS/NBP
highly regioselective!
undesired halogenation
suppressed by Rh(III)
Y
het
DG
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