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Dual Role of Rh(III) Catalyst Enables Regioselective Halogenation of (Electron-Rich) Heterocycles

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Supporting Information

ABSTRACT: The Rh(III)-catalyzed selective bromination and iodination of electron-rich heterocycles is reported. Kinetic investigations show that Rh plays a dual role in the bromination, catalyzing the directed halogenation and preventing the inherent halogenation of these substrates. As a result, this method gives highly selective access to valuable halogenated heterocycles with regiochemistry complementary 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] Halogenated compounds comprise a major class of building blocks for the synthesis of heterocycles, 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, direct halogenation to yield other isomers is often challenging and requires harsh reaction conditions and/or many synthetic steps. One prominent strategy is directed *ortho* metalation (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 past few years, a plethora of reports on the halogenation of benzene derivatives have been published, 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 Pd catalyst and molecular I_2 as the oxidant.[6r] In that excellent report, pyrazoles, oxazoles, thiazoles, and pyridines could be used as suitable substrates. However, no directed halogenation exists for the synthesis of electron-rich heterocycles like furans and thiophenes that can override the inherent reactivity for these substrates (Figure 1).[8]

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-dichloroethane (DCE) as the solvent, we were able to get the

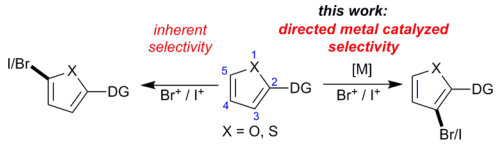
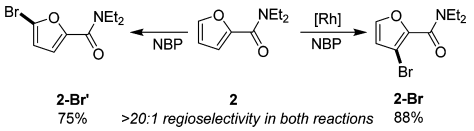


Figure 1. Switch of selectivity.

desired product in a yield of 84% (see Supporting Information (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*-bromophthalimide (NBP) instead of NBS, 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** is also effective. 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 Rh-Catalyzed Halogenation Compared to the Standard Reactivity



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

With the optimized conditions in hand, we examined the scope of different heterocycles with different substitution patterns, bearing the directing group (DG) 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

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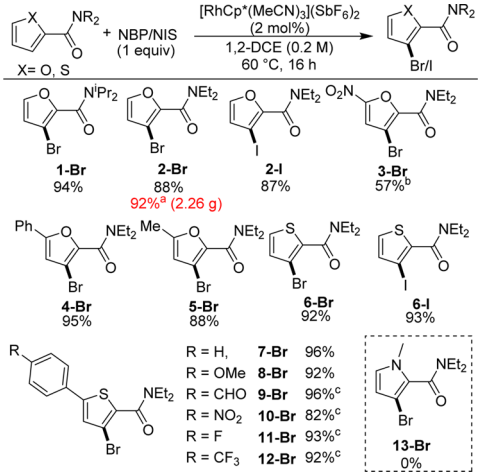
Table 1. Scope of the Halogenation of Furans and Thiophenes with the Directing Group in the 2-Position



Unless otherwise noted, reactions were performed on a 0.4 mmol scale under air; isolated yields are given. [a]Reaction was performed on a 10 mmol scale. [b]Reaction temperature was 100 °C, and 1.2 equiv of NBP was used. [c]Reaction was performed on a 0.2 mmol scale.

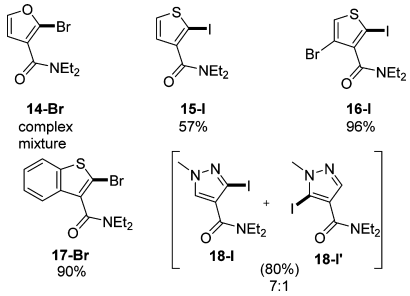
the furan, the reactivity decreased significantly, and higher temperatures were needed to provide **3-Br** in an acceptable yield of 57%. Methyl and phenyl substituents were readily tolerated, and the yield of the products was 88% for **5-Br** and 95% for **4-Br**. Product **5-Br** is a good example for the efficiency of the Rh(III)-catalyzed reaction, suppressing two different side reactions which were found in the control reaction without any catalyst: bromination in the 4-position occurred in 14% isolated yield, resulting most likely from an electrophilic pathway, and 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 gave 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.

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

In comparison to furans with the amide moiety in the 3-position, thiophenes like **15** and **16** could be iodinated in moderate to excellent yields. 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 a 7:1 mixture of both possible regioisomers in a combined yield of 80%.

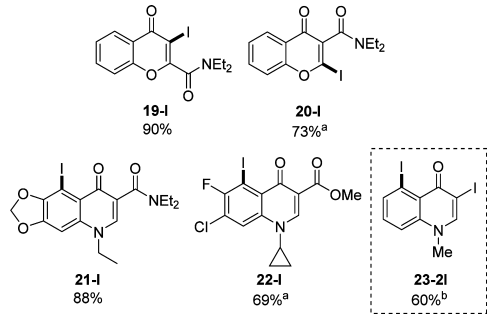
Other important benzannulated heterocycles were also tested under our reaction conditions (Table 3).[14] Chromones **19** and **20** and the amide derivative of oxolinic acid **21**, an antibiotic of the quinolone class, underwent iodination in good yields. Interestingly, in the quinolone examples, iodination 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, and activation of the ring ketone group as a DG through the nitrogen, which could be viewed as a vinylogous amide. In addition to amides, ester **22** (the free acid is a precursor

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: 2 mol% $[RhCp^*(MeCN)_3](SbF_6)_2$, 1 equiv of NBP/NIS, 0.2 M 1,2-DCE.

Table 3. Iodination of Other Heterocycles and Arenes

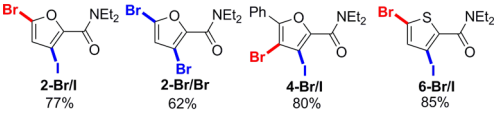


All reaction were performed on a 0.4 mmol scale. Conditions: 2 mol% $[RhCp^*(MeCN)_3](SbF_6)_2$, 1 equiv of NBP/NIS, 0.2 M 1,2-DCE. [a]Reaction temperature was 100 °C. [b]5 mol% $[RhCp^*(MeCN)_3](SbF_6)_2$.

of Ciprofloxaxin, another quinolone-type antibiotic) also underwent iodination, but in a lower yield of 69%. To prove that the DG is the vinylogous amide and the amide or ester function is not important, 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.

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]

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.

The yields for this one-pot procedure were generally very good; only for product **2-Br/Br**, where two brominations occurred, was a modest yield of 67% observed. Due to the presence of the Rh catalyst in this procedure, the second halogenation usually required longer reaction times (see also Figure 2). A key feature is that, for substrates with a blocked 5-position, even the 3,4-dihalogenation occurred in good yield. Thus, this method allows the synthesis of the completely substituted furan **4-Br/I**.

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To better understand the origin of the high levels of regioselectivity in the Rh-catalyzed bromination of furan and thiophene, we conducted 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 Rh catalyst (Figure 2).

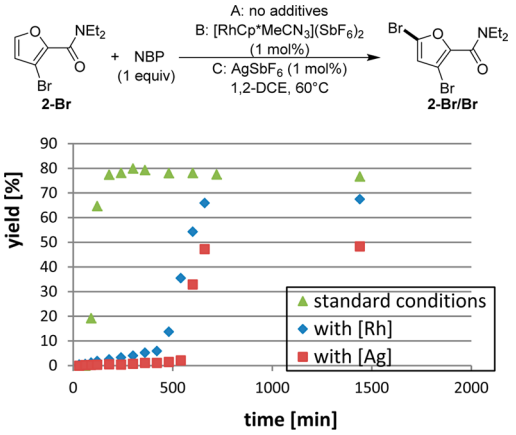


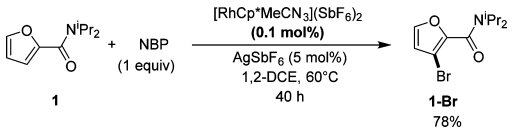
Figure 2. Inherent reactivity in the absence and in the presence of $[RhCp^*(MeCN)_3](SbF_6)_2$. Yield determined by GC analysis.

The inherent, uncatalyzed bromination at the 5-position in the absence of Rh showed an induction period, suggesting that the substrate does not react directly 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 Rh catalyst, the rate of the inherent bromination at the 5-position is dramatically decreased. Presumably, the Rh 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). We were also 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-positions available for halogenation, the Rh catalyst plays two roles in ensuring high levels of regioselectivity. On one hand, Rh 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.

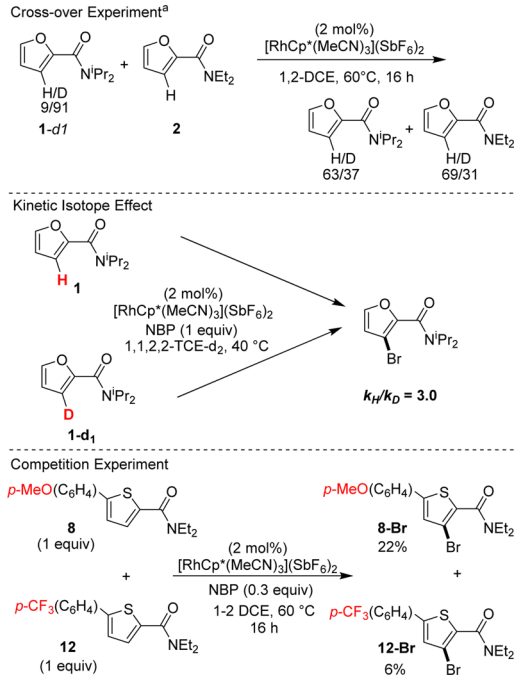
We thought that the complexation of bromide by the Rh catalyst is also the major decomposition pathway of the active catalyst in our standard reaction. To prevent this pathway, we performed the bromination of **1** in the presence of 5 mol% $AgSbF_6$ as an additive to remove the bromide. Indeed, it was 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 were performed (Scheme 4). To elucidate

Scheme 3. Bromination of 1 in the Presence of $AgSbF_6$



Scheme 4. Mechanistic Experiments[a]



[a]Reaction conditions: 0.20 mmol of **2** and 0.17 mmol of **1**-d_1. Deuterium distribution was analyzed by electrospray ionization.

the nature of the C−H activation step, we conducted a crossover experiment between deuterium-enriched diisopropylamide **1**-d_1 and diethylamide **2**. In the presence of 2 mol% of the Rh catalyst and no other additives, significant deuterium scrambling 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 MeOD was used as an external deuterium source (see SI).

A significant kinetic isotope effect (KIE) was observed when the rate constants of the reaction of **1** and **1**-d_1 were measured, 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, the large KIE argues against this pathway.[16] A concerted metalation−deprotonation pathway may take place, with the amide moiety of the substrate acting as a base. However, at this point, neither of these two mechanisms can be ruled out.

Following the C−H activation event, two alternative scenarios seem plausible: (i) oxidation of the Rh(III) intermediate with the halogenating agent to generate a Rh(V) species, which releases the desired product after reductive elimination, or (ii) 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 operative in other catalytic transformations. The benzannulated six-membered heterocycles chromones and quinolones were also successfully iodinated.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic data, and mechanistic experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(11) Note that NaOAc suppresses the reaction, while HOAc and $Cu(OAc)_2$ have no influence on the reactivity, probably because many free OAc anions coordinate to the Rh and therefore diminish its reactivity.

(12) In contrast to bromination, iodination was much slower in the absence of the Rh catalyst. NIS, which is commercially available, unlike *N*-iodophthalimide, showed a reactivity similar to that of NBP and thus was the 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, iodination was more effective. Bromination with NBP often led to only lower conversions to the desired product.

(15) The Rh-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 would occur.

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