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Ruthenium-catalyzed *ortho*-C–H halogenations of benzamides†

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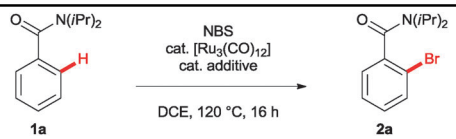
$[Ru_3(CO)_{12}]$ and $AgO_2C(1\text{-Ad})$ enabled the first ruthenium-catalyzed intermolecular halogenations of arenes *via* C–H activation. Thereby, brominations and iodinations of electron-rich and electron-deficient benzamides were achieved in a highly selective fashion.

Aromatic halides are key intermediates in organic synthesis, and have been broadly utilized in natural product synthesis, material sciences and medicinal chemistry.[1] As a consequence, the development of efficient and selective methods for their syntheses continues to be of crucial importance. The most useful strategies rely on the electrophilic aromatic substitution, the Sandmeyer reaction or the directed *ortho*-lithiation approach.[2] Unfortunately, these methods face considerable limitations, including tedious and/or hazardous reaction procedures, poor site-selectivities, and harsh reaction conditions, resulting in low chemo-selectivities. In recent years, metal-catalyzed C–H activation has emerged as an increasingly viable tool for C–C and C–Het formation.[3] In this context, methods for the palladium-catalyzed chelation-assisted direct C–H functionalization with electrophilic halogenating reagents have been developed by Sanford[4] and Yu[5] among others.[6,7] Furthermore, Glorius very recently demonstrated $[RhCp^*Cl_2]_2$ to be a competent catalyst for halogenation of arenes.[8] In recent years, considerably less expensive[9] ruthenium complexes[10] have been identified as powerful catalysts for the oxidative transformation of otherwise unreactive C–H bonds into C–C,[11] C–O[12] or C–N[13] bonds.[14] In strict contrast, ruthenium-catalyzed intermolecular C–Hal bond forming processes are unfortunately not available. Herein, we wish to disclose ruthenium-catalyzed C–H halogenation on synthetically useful benzamides, which proceeded with excellent site- and chemo-selectivities.

We initiated our studies by exploring various reaction conditions for the desired bromination of benzamide **1a**. After considerable optimization, we were pleased to observe that the desired product **2a** was obtained in high yields using $Ru_3(CO)_{12}$ as the catalyst and PivOH or 1-AdCO_2H[15] as stoichiometric additives (Table 1, entries 1–5 and Table S1 in the ESI†). Interestingly, the formation of halogenated product **2a** was significantly improved when using silver(I) salts as the catalytic additives (entries 6–16), with $AgO_2C(1\text{-Ad})$ furnishing optimal results (entry 15).[16] It is noteworthy that the use of additional oxidants, such as copper(II) or silver(I) salts, was not required.[17]

Table 1 Optimization of the catalyzed direct bromination[a]



1a **2a**

Entry	Additive (equiv.)	**2a**[b] (%)
1	—	27
2[c]	—	<2
3[c]	PivOH (2.0)	<2
4	PivOH (2.0)	57
5	1-AdCO_2H (2.0)	57
6	PivOH (0.2)	19
7	CsOAc (0.2)	24
8	KPF_6 (0.2)	22
9	$AgSbF_6$ (0.2)	18
10	AgCl (0.2)	20
11	Ag_2CO_3 (0.2)	34
12	AgO_2CCF_3 (0.2)	41
13	AgOAc (0.2)	58
14	AgOPiv (0.2)	60
15	**$AgO_2C(1\text{-Ad})$ (0.2)**	**64, 60**[d]
16[c]	$AgO_2C(1\text{-Ad})$ (0.2)	<2

[a] Reaction conditions: **1a** (0.5 mmol), NBS (1.0 mmol), $[Ru_3(CO)_{12}]$ (3.3 mol%), additive, DCE (2.0 mL), 120 °C, 16 h. [b] ^{1}H-NMR conversion with 1,3,5-trimethoxybenzene as the internal standard. [c] Without $[Ru_3(CO)_{12}]$. [d] Isolated yield.

With the optimized conditions in hand, we probed the scope of the C–H bromination with differently decorated benzamides **1** (Scheme 1). Substrate **1b** afforded the desired product **2b** in an excellent yield, even at a lower reaction temperature. Intramolecular competition experiments with *meta*-substituted arene **1c** bearing two chemically inequivalent *ortho* C–H bonds showed the less hindered C–H bond to be primarily brominated. In contrast, the

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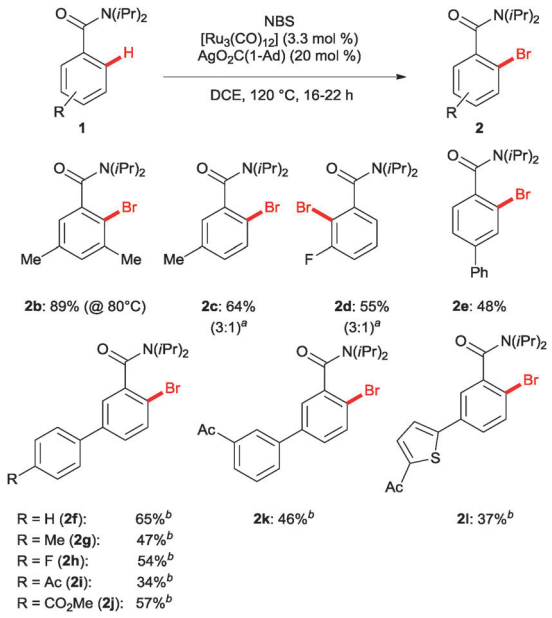
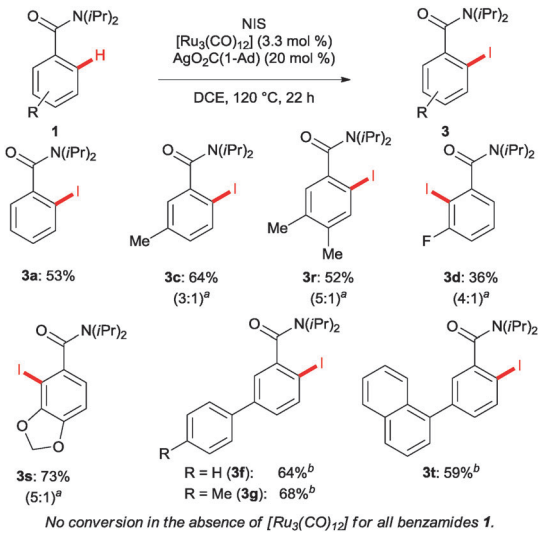
† Electronic supplementary information (ESI) available: Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra for products. See DOI: 10.1039/c3cc47852a



Scheme 1 Ruthenium-catalyzed C–H bromination on benzamides **1**: [a] isolated yields of the major isomer. Ratio of regioisomers (major : minor) of the crude reaction mixture as determined by GC analysis in parenthesis. [b] Only one isomer was observed by GC analysis.



Scheme 3 Ruthenium-catalyzed C–H iodination: [a] isolated yields of the major isomer. Ratio of regioisomers (major : minor) of the crude reaction mixture as determined by GC analysis in parenthesis. [b] Only one isomer was observed by GC analysis.

electron-deficient benzamide **1d** predominantly gave isomer **2d**, likely because of a secondary directing group effect.[18] The C–H functionalizations of substrates bearing additional (hetero)aromatic moieties proceeded with excellent site-selectivities in the *ortho*-position to the amide. Thereby, synthetically useful heterocycles (**2l**) and functional groups, such as acetyl (**2i** and **2k**) or ester (**2j**), were tolerated by the catalyst.[19]

The analogous C–H iodinations could be accomplished with NIS in lieu of NBS. Here, we first examined the influence of different amide *N*-substituents on the efficacy of the corresponding iodination (Scheme 2). Thus, a variety of benzamides **1** provided the desired iodinated products **3**, while control experiments demonstrated that omission of the ruthenium(0) catalyst proved to be detrimental.

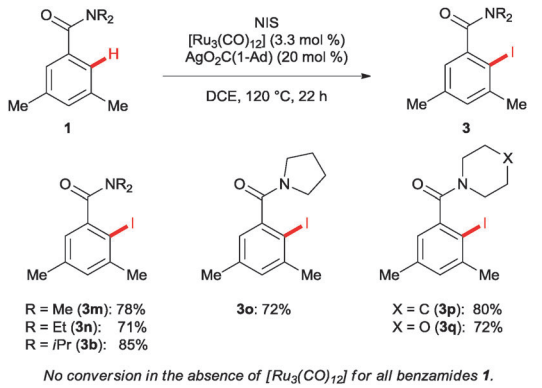
The versatile ruthenium(0) catalyst displayed a broad substrate scope and allowed for C–H iodinations of differently substituted arenes **1** (Scheme 3). Importantly, *meta*-substituted arenes **1** gave the desired products **3** with useful site-selectivities. As was observed for the bromination (*vide supra*), the C–H iodination was viable neither in the absence of the ruthenium(0) catalyst nor of the additive AgO_2C(1-Ad) for all substrates **1a–1t.**

In consideration of the unique reactivity profile of the novel ruthenium(0) catalyst, we performed mechanistic studies to delineate its mode of action.

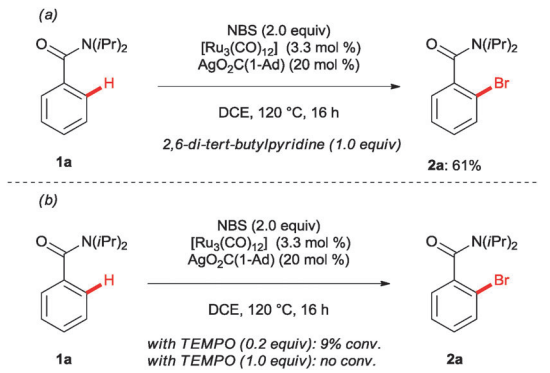
To this end, Brønsted-acid (co)catalysis could be ruled out by successfully performing the C–H bromination in the presence of stoichiometric amounts of 2,6-di-*tert*-butylpyridine[20] (Scheme 4a). In contrast, the addition of TEMPO inhibited the catalytic reaction (Scheme 4b), which could be rationalized in terms of SET-type processes being operative.

Furthermore, the catalytic C–H functionalization in the presence of isotopically labelled additive $[D]_1$-**4** highlighted a reversible C–H ruthenation event (Scheme 5 and Scheme S1 in the ESI†).

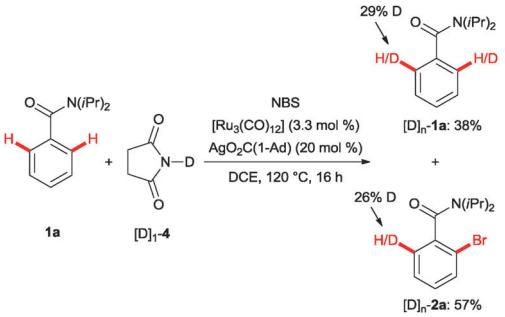
In good agreement with these observations, the initial reaction rate determined by independent experiments with substrates



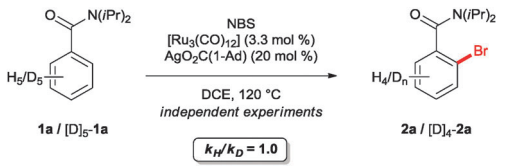
Scheme 2 Effect of *N*-substituents on C–H iodinations.



Scheme 4 Effect of added (a) 2,6-di-*tert*-butylpyridine or (b) TEMPO.



Scheme 5 C–H functionalization with labelled compound $[D]_1$-**4**.



Scheme 6 Kinetic isotope effect studies.

1a and $[D]_5$-**1a** did not reveal a significant kinetic isotope effect (KIE, $k_H/k_D \approx 1.0$),[21] hence being indicative of the C–H cleavage not to be kinetically relevant (Scheme 6).

In summary, we have reported on the first ruthenium-catalyzed *ortho*-selective C–H halogenations on arenes through C–H activation. Thus, a catalytic system comprising of $[Ru_3(CO)_{12}]$ and $AgO_2C(1\text{-Ad})$ allowed site-selective brominations and iodinations on amides with ample scope and excellent functional group tolerance. Preliminary mechanistic studies provided evidence for a reversible C–H metalation event.

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