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

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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, ruthenium-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 oxidative transformation of otherwise unreactive C–H bonds with electrophilic halogenating reagents have been developed by Sanford4 and Yu5 among others.6,7 Furthermore, Glorius very recently demonstrated [RhCp*Cl2]2 to be a competent catalyst for 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.8 In recent years, considerably less expensive9 ruthenium complexes10 have been identified as powerful catalysts for the oxidative transformation of otherwise unreactive C–H bonds into C–C,11 C–O12 or C–N13 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 Ru3(CO)12 as the catalyst in PivOH or 1-AdCO2H15 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 AgO2C(1-Ad) furnishing optimal results (entry 15).16 It is noteworthy that the use of additional oxidants, such as copper(a) or silver(i) salts, was not required.17

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

Table 1 Optimization of the catalyzed direct brominationa

| Entry | Additive (equiv.) | 2a (%) |
|-------|------------------|--------|
| 1     | —                | 27     |
| 2c    | —                | <2     |
| 3c    | PivOH (2.0)      | <2     |
| 4     | PivOH (2.0)      | 57     |
| 5     | 1-AdCO2H (2.0)   | 57     |
| 6     | PivOH (0.2)      | 19     |
| 7     | CsOAc (0.2)      | 24     |
| 8     | KPF6 (0.2)       | 22     |
| 9     | AgSbF6 (0.2)     | 18     |
| 10    | AgClO2 (0.2)     | 20     |
| 11    | AgCO2 (0.2)      | 34     |
| 12    | Ag2CO3 (0.2)     | 41     |
| 13    | AgOAc (0.2)      | 58     |
| 14    | AgOPiv (0.2)     | 60     |
| 15    | AgO2C(1-Ad) (0.2) | 64, 60 |
| 16f   | AgO2C(1-Ad) (0.2) | <2     |

a Reaction conditions: 1a (0.5 mmol), NBS (1.0 mmol), [Ru3(CO)12] (3.3 mol%), additive, DCE (2.0 mL), 120 °C, 16 h. b H-NMR conversion with 1,3,5-trimethoxybenzene as the internal standard. c Without [Ru3(CO)12]. d Isolated yield.
electron-deficient benzamide 1d predominantly gave isomer 2d, likely because of a secondary directing group effect.\textsuperscript{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.\textsuperscript{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\textsubscript{2}C(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\textsuperscript{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\textsuperscript{†}).

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

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

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

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

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

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\[ \text{Scheme 1 Ruthenium-catalyzed C–H bromination on benzamides 1:} \]
\[ \text{Scheme 2 Effect of N-substituents on C–H iodinations.} \]
\[ \text{Scheme 3 Ruthenium-catalyzed C–H iodination:} \]
\[ \text{Scheme 4 Effect of added (a) 2,6-di-tert-butylpyridine or (b) TEMPO.} \]
1a and [D]$_2$-1a did not reveal a significant kinetic isotope effect (KIE, $k_{H}/k_{D} \approx 1.0$),$^{11}$ 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 Ag$_2$O$_2$(Tf$_2$N)$_2$ 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 metatation event.

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Notes and references

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17 For detailed information, see the ESIF.

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