ORGANIC LETTERS

2013
Vol. 15, No. 4
928–931

Cross Dehydrogenative Coupling via Base-Promoted Homolytic Aromatic Substitution (BHAS): Synthesis of Fluorenones and Xanthones

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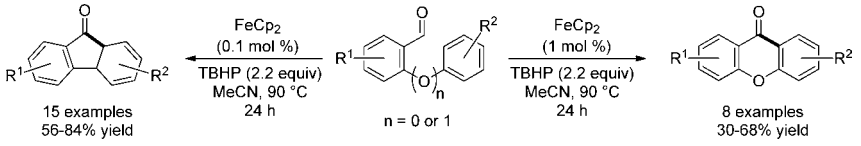
Received January 11, 2013

ABSTRACT



Cross dehydrogenative coupling reactions occurring via base-promoted homolytic aromatic substitutions (BHASs) are reported. Fluorenones and xanthones are readily prepared via CDC starting with readily available *ortho*-formyl biphenyls and *ortho*-formyl biphenylethers, respectively. The commercially available and cheap *t*BuOOH is used as an oxidant. Initiation of the radical chain reaction is best achieved with small amounts of $FeCp_2$ (0.1 or 1 mol %).

Development of selective and efficient C−C bond forming reactions is of great importance in organic chemistry. No doubt, cross-coupling with two prefunctionalized substrates with the help of transition metal (TM) catalysts ranks as one of the most powerful approaches for C−C bond formation.[1] As a further development, TM-catalyzed C−H bond activation with subsequent C−C bond formation has gained great attention recently[2] and cross-dehydrogenative coupling (CDC) where prefunctionalization of the reacting partners is not necessary has emerged as an even more atom economic approach for the construction of C−C bonds.[3] $C(sp^2)$−$C(sp^2)$ bond formation, in particular C−H arylation, has been most intensively investigated along that line. Radical chemistry offers a valuable alternative to TM-based arylations.[4] Recently, a series of papers on TM-free direct intra- and intermolecular radical C−H arylations has appeared in the literature.[5,6] These processes likely proceed via base-promoted homolytic aromatic substitution (BHAS, Scheme 1).[7]

Intra- or intermolecular aryl radical addition to an arene leads to the corresponding cyclohexadienyl adduct radical which upon deprotonation with an external *base* provides a biaryl radical anion. This species acts as a single electron transfer (SET) reagent for reduction of the starting aryl-iodide to generate another corresponding aryl radical. Thereby the radical chain reaction is sustained.[7]

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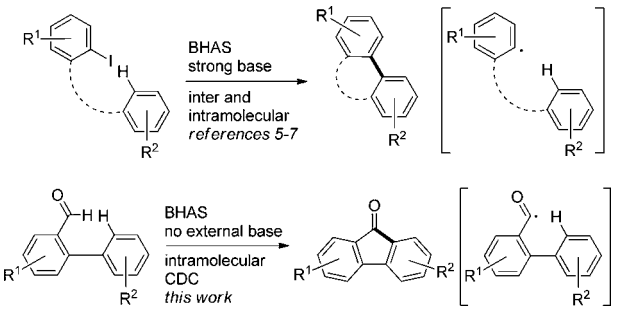
10.1021/ol4000857
Published on Web 02/01/2013

Scheme 1. Base-Promoted Homolytic Aromatic Substitution



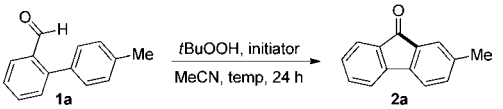
However, in all these examples a prefunctionalized radical precursor (mostly an aryl iodide) has to be chosen as starting material. Herein we present intramolecular BHAS of various biphenyl-2-carboxaldehydes which proceed via acyl radicals[8] to give the corresponding fluorenones representing a radical cross dehydrogenative $C(sp^2)-C(sp^2)$ bond forming process.[9,10] In contrast to the known BHAS processes, a halide as a radical leaving group and an external strong base are not necessary thereby improving the economy of the overall transformation.

As a substrate for optimization studies we chose biphenyl-2-carboxyaldehyde **1a**. The *tert*-butoxyl radical is known to efficiently abstract the hydrogen atom of the carbonyl in aldehydes, and the commercially available *t*BuOOH is readily reduced by SET to the *tert*-butoxyl radical and the basic hydroxide anion. Hence, this cheap reagent should be well suited to act as a reagent for the planned BHAS reactions. We tested radical CDC of **1a** to give fluorenone (**2a**) with *t*BuOOH (aq) as the oxidant (Table 1).

In the absence of an external radical initiator with 2.2 equiv of *t*BuOOH at 90 °C, we obtained **2a** in 41% yield (entry 4). Reducing the amount of *t*BuOOH led to lower yields (entries 1−3).

The yield was higher with nonaqueous *t*BuOOH; however, we faced difficulties in reproducing results, and yields varied between 31 and 63% (entry 5). This is due to the initiation step which is probably mediated with traces of TMs.[11] We therefore tested the reaction in the presence of a small amounts of TMs and found that $FeCp_2$ performs well (entry 6). Good results were achieved with 0.1 mol % of $FeCp_2$ (72%, entry 13); however yields varied. Upon adding *t*BuOOH in two batches a reproducible 73% yield was obtained (entry 14). Increasing (53% with 1 mol % $FeCp_2$ under otherwise identical conditions) or decreasing (~55% NMR yield with 0.02 mol % of $FeCp_2$) the initiator loading gave worse results, and other Fe(II)-salts also gave good yields (entries 7−9). A good yield was achieved with $Fe(OAc)_2$; however, due to the low solubility of the acetate in CH_3CN, this result was difficult to reproduce. Therefore, the $FeCp_2$-initiator was regarded as the best Fe-derivative among this series. CuI or $Pd(OAc)_2$ provided lower yields (entries 10, 11). A good result was also achieved by using 0.5 mol % of Bu_4NI which is well-known to mediate radical reactions in the presence of *t*BuOOH (entry 12).[12] *t*BuONNO*t*Bu could also be used to initiate this reaction. However, as compared to $FeCp_2$ a significantly higher initiator loading had to be used (entry 15), and at lower temperature the chain was not efficient (entry 16). With *t*BuOO*t*Bu in the absence of *t*BuOOH, only trace amounts of product were formed (entry 17). Finally, MeCN was found to be the best suited solvent as compared to other solvents such as tetrahydrofuran, dichloroethane, dimethylacetamide, or benzotrifluoride.

Table 1. Reaction Optimization Using **1a** as a Substrate



1a **2a**

entry	temp (°C)	*t*BuOOH (equiv)	initiator (mol %)	yield[a] (%)
1	90	2.0 (aq)	–	19−31[b]
2	90	1.0 (aq)	–	21
3	90	0.1 (aq)	–	4
4	90	2.2 (aq)	–	41
5	90	2.2 (dec)	–	31−63[b]
6	90	2.2 (dec)	$FeCp_2$ (0.5)	66
7	90	2.2 (dec)	$FeCl_2$ (0.5)	62
8	90	2.2 (dec)	$Fe(OAc)_2$ (0.5)	73
9	90	2.2 (dec)	$FeSO_4$ (0.5)	60
10	90	2.2 (dec)	CuI (0.5)	26
11	90	2.2 (dec)	$Pd(OAc)_2$ (0.5)	22
12	90	2.2 (dec)	Bu_4NI (0.5)	64
13	90	2.2 (dec)	$FeCp_2$ (0.1)	60−72[b]
14	90	2.2 (dec)	$FeCp_2$ (0.1)	73[c]
15	90	2.2 (dec)	*t*BuONNO*t*Bu (10)	52
16	50	2.2 (dec)	*t*BuONNO*t*Bu (10)	17
17	120	–	*t*BuOO*t*Bu (100)	traces

[a] Determined by ^1H NMR using an internal standard. [b] Difficult to reproduce, yields in the range given were obtained. [c] *t*BuOOH added in two batches (aq = aqueous, dec = decane: used as a 5.5 M sol. in dec.).

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(10) TM-free fluorenone synthesis: (a) Denney, D. B.; Klemchuk, P. P. *J. Am. Chem. Soc.* **1958**, *80*, 3289–3290. (b) Barluenga, J.; Trincado, M.; Rubio, E.; González, J. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 3140–3143. (c) Shi, Z.; Glorius, F. *Chem. Sci.* **2013**, *4*, 829–833. (d) Matcha, K.; Antonchick, A. P. *Angew. Chem., Int. Ed.* **2013**, *early view*, DOI: 10.1002/anie.201208851.

(11) A similar initiation and chain propagation step was recently suggested for a radical arene trifluoromethylation: Ji, Y.; Brueckl, T.; Baxter, R. D.; Fujiwara, Y.; Seiple, I. B.; Su, S.; Blackmond, D. G.; Baran, P. S. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 14411–14415.

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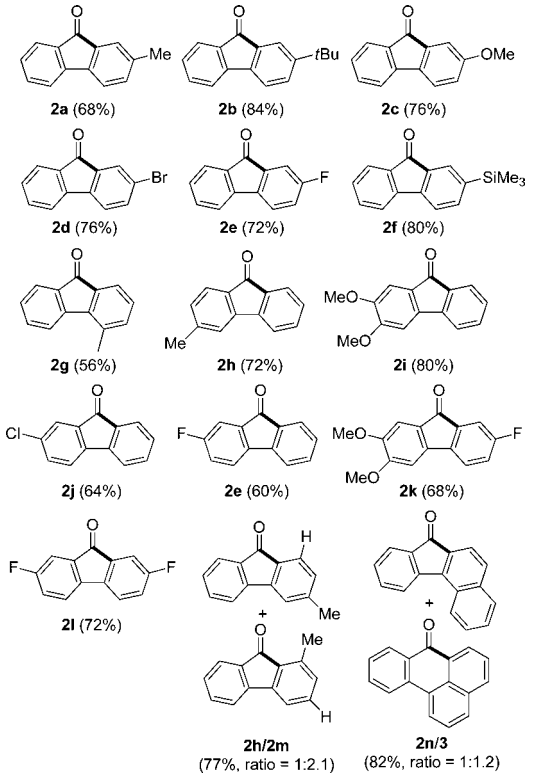
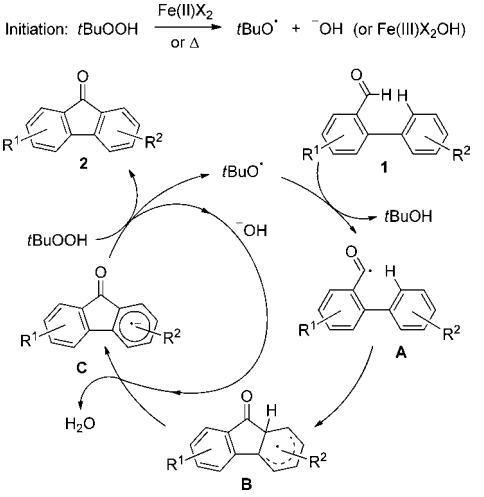


Figure 1. Fluorenone synthesis: substrate scope (isolated yields).

To document the substrate scope, various formylated biaryls were reacted under optimized conditions (2.2 equiv of *t*BuOOH, 0.1 mol % $FeCp_2$, CH_3CN) to the corresponding fluorenones (Figure 1). Electron-donating and -withdrawing substituents at the *para*-position of the radical accepting arene in the biphenyl moiety were tolerated, and fluorenones **2b**–**f** were isolated in good yields (68–84%). As expected for a radical process, the *meta*-substituted congener reacted with low regioselectivity (see **2m**). We further showed that the formyl carrying arene moiety in the biphenyl substrate can bear electron-donating and -withdrawing substituents (**2h**–**j** and **2e**) and also substrates, where both arenes carry substituents, provided the corresponding CDC products in good yields (**2k**, **2l**). Interestingly, the naphthyl derivative afforded, along with the targeted fluorenone **2n**, ketone **3** in good overall yield (82%).

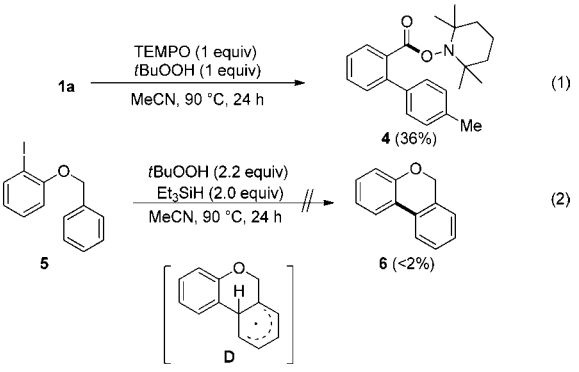
The suggested mechanism for the fluorenone synthesis is depicted in Scheme 2. Initiation occurs by reducing *t*BuOOH with FeX_2 to give the *tert*-butoxyl radical along with an Fe(III)-complex. The *tert*-butoxyl radical then abstracts the H-atom from the aldehyde to give acyl radical **A** which attacks the arene to generate the cyclohexadienyl radical **B**.[13] Deprotonation with the basic hydroxide anion

Scheme 2. Suggested Mechanism



leads to the biaryl radical anion **C**. Deprotonation is facilitated by the neighboring carbonyl group. Indeed, it was previously shown that cyclohexadienyl radicals bearing acidifying nitrile or carbonyl functionalities are deprotonated by a weak base.[14] **C** then reduces *t*BuOOH by SET to provide fluorenone **2** and the chain propagating *tert*-butoxyl radical along with the basic hydroxide anion.[11] We assume that as side reactions the biaryl radical anion **C** and the cyclohexadienyl radical **B** can also reduce the Fe(III)-complex generated in the initiation step thereby regenerating the initiator.[15] This is likely the reason why only very small amounts of the radical initiator are necessary in these chain reactions.

Experimental proof for the involvement of acyl radicals was obtained by running the reaction in the presence of TEMPO (1 equiv). The TEMPO-ester **4** was isolated in 36% yield, and **2a** was not formed (eq 1). Moreover, in order to evaluate the possibility whether cyclohexadienyl radicals of type **B** can reduce *t*BuOOH by SET prior to deprotonation, we ran a control experiment on iodide **5** which is a typical substrate in BHAS reactions.[7]



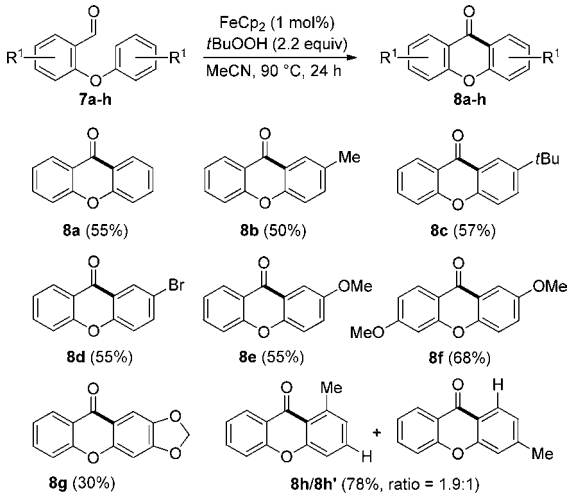
To generate the necessary aryl radical from the iodide we added Et_3SiH which is known to be readily converted to

(13) Acyl radicals are known to react intramolecularily with heteroarenes: (a) Miranda, L. D.; Cruz-Almanza, R.; Pavón, M.; Alva, E.; Muchowski, J. M. *Tetrahedron Lett.* **1999**, *40*, 7153–7157. (b) Allin, S. M.; Barton, W. R. S.; Bowman, W. R.; McInally, T. *Tetrahedron Lett.* **2001**, *42*, 7887–7890. (d) A review on intermolcular acyl radical additions to heteroarenes: Minisci, F. *Synthesis* **1973**, 1–24. Minisci, F. *Top. Curr. Chem.* **1976**, *62*, 1–48.

(14) Wang, C.; Russell, G. A.; Trahanovsky, W. S. *J. Org. Chem.* **1998**, *63*, 9956–9959.

(15) These processes can only be side reactions since we obtained in some cases good results also in the absence of the Fe-initiator (see Table 1).

Scheme 3. Xanthone Synthesis via Radical CDC (isolated yields)



Et_3Si radicals in the presence of *tert*-butoxyl radicals. The Si-centered radicals provide aryl radicals by iodine abstraction from the corresponding aryl iodide. As shown in eq 2, the targeted product **6** was not identified by GC-analysis.[16] This experiment supports our assumption that cyclohexadienyl radical **D**, which is a reasonable model for **B**, does not efficiently reduce *t*BuOOH.

We also tested whether the radical BHAS can be applied to other CDC reactions and found that xanthones are readily prepared under similar conditions from the aldehydes **7a**–**h**. Chains were shorter, and a higher initiator loading (1 mol % $FeCp_2$) was necessary. As compared to the fluorenone synthesis, generally lower yields were achieved (Scheme 3). As side products we always identified the corresponding *ortho*-hydroxybenzophenone derivatives, resulting from *ipso* attack of the acyl radical and subsequent cleavage of the C–O bond providing stabilized phenoxyl radicals. We found that substrates bearing electron-donating and -withdrawing substituents at the *para*-position of the radical accepting arene moiety afforded similar yields showing that electronic effects exerted by the acyl radical acceptor on the cyclization are weak (**8a**–**e**). The *meta*-methyl derivative gave the two regioisomeric xanthones **8h** and **8h′** in a 1.9:1 ratio indicating the radical nature of the cyclization process. Surprisingly, **8g** was isolated as a single regioisomer albeit in a moderate yield.

In summary, we have presented CDC reactions occurring via base-promoted homolytic aromatic substitutions (BHASs). BHASs have gained great attention during the past four years.[6,7] However, all of these reports deal with the use of aryl iodides as radical precursors. Moreover, in the known BHAS reactions a stoichiometric amount of base is necessary and reactions are generally conducted under harsh conditions. Our protocol does not require any additional base, and the commercially available oxidant (*t*BuOOH) is cheap. We showed that radical reactions are very efficient since only a small amount of initiator is necessary to run these processes (long chains) which are experimentally easy to conduct. The concept presented herein gives some guidelines for the design of new BHASs.

Acknowledgment. This work was supported by the program "Sustainable Chemical Synthesis (SusChemSys)" which is cofinanced by the European Regional Development Fund (ERDF) and the state of North Rhine-Westphalia, Germany, under the Operational Program "Regional Competitiveness and Employment" 2007–2013.

Supporting Information Available. Experimental details and characterization data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

(16) To make sure that the Fe-initiator does not interfere with the Si-chemistry we ran the experiment in the absence of the $FeCp_2$ initiator. Repeating the reaction with $FeCp_2$ under otherwise identical conditions gave **6** in 14% yield (determined by GC). This control experiment indicates that the cyclohexadienyl radical **D** gets slowly oxidized by the Fe(III)-complex but not by *t*BuOOH. However, that chain reaction is not efficient.

The authors declare no competing financial interest.