Radical Cyclizations

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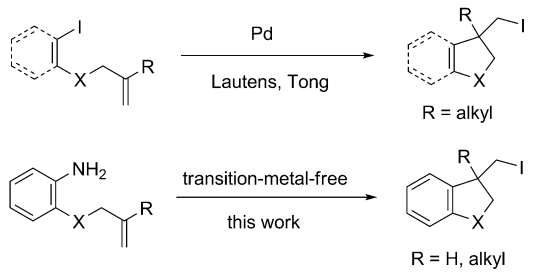
Cyclizing Radical Carboiodination, Carbotelluration, and Carboaminoxylation of Aryl Amines**

*Marcel Hartmann and Armido Studer**

Abstract: *Radical carboiodination of various aryl amines is reported. Aryl diazonium salts, generated in situ from the corresponding aryl amines, are reacted with Bu_4NI to provide the corresponding aryl radicals which undergo 5-exo or 6-exo cyclization. Iodine abstraction eventually affords the carboiodinated products in good to excellent yields. If TEMPO is added, the cascade provides the cyclized carboaminoxylation products. Running the reaction in the presence of PhTeTePh affords the phenyltellurated cyclized products.*

Palladium-mediated radical carboiodinations of alkenes using activated alkyl iodides are known.[1a] Recently this chemistry was extended to aryl iodides by Lautens and Tong.[1b–e] They showed that appropriately substituted aryl iodides can be isomerized in good yields to the corresponding cyclic alkyl iodides (Scheme 1). Experimental and theoretical



Scheme 1. Carboiodinations.

studies revealed that these cyclizations occur through the migrative insertion of the corresponding aryl–Pd intermediates.[2] Stimulated by these studies we embarked a program on cyclizing radical carboiodinations using aryl amines as starting materials. One advantage over the existing methods is that with the radical approach it should be possible to conduct the carboiodination under transition-metal-free conditions. Moreover, a quaternary C center next to the C–I bond in the product iodide is not necessary since in the radical pathway β-H elimination, which is a problem in the Pd-mediated process, will not occur.

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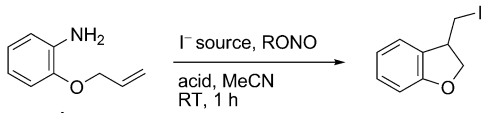
We decided to start with aryl amines, which are transformed in situ to the corresponding aryl diazonium salts, as efficient C radical precursors.[3] Aryl diazonium salts have been successfully used in radical cyclization reactions induced by single-electron-transfer (SET) reagents[4] and also sodium iodide mediated reactions to give the corresponding iododediazonation products have been reported.[5] However, not every aryl amine can be readily transformed to the corresponding aryl diazonium salt due to its limited stability and due to problems occurring during isolation. Moreover, some aryl diazonium salts are explosive and care has to be taken during isolation and storage. Therefore, generating aryl diazonium salts in situ under conditions where they can undergo further reaction directly might solve these problems.

In fact, aryl amines have been elegantly used by Wang and co-workers in radical arylations in the in situ generation of the corresponding aryl diazonium salts.[6] It is important to note that carboiodination cannot be achieved by radical iodine transfer chemistry starting with aryl iodides. This is because the C–I bond in aryl iodides is stronger than that in alkyl iodides and because the aryl radicals are high in energy. Therefore, an alkyl radical cannot abstract an iodine atom from an aryl iodide.[7] Herein we report useful radical carboiodinations of various aryl amines and will further show that the concept can be also applied to carbotellurations and carboaminoxylations.

Optimization studies were conducted using aryl amine **1a** to provide cyclized alkyl iodide **2a** (Table 1). Reactions were run in acetonitrile and isoamyl nitrite (1.5 equiv) served as the

Table 1: Reaction optimization.



1a **2a**

Entry	I^- source (equiv)	R (equiv)	Acid (equiv)	Yield [%]
1	NaI (1.5)	isoamyl (1.5)	$MeSO_3H$ (1.1)	68
2	KI (1.5)	isoamyl (1.5)	$MeSO_3H$ (1.1)	77
3	CsI (1.5)	isoamyl (1.5)	$MeSO_3H$ (1.1)	94
4	**Bu_4NI (1.5)**	**isoamyl (1.5)**	**$MeSO_3H$ (1.1)**	**99**
5	Bu_4NI (1.1)	isoamyl (1.5)	$MeSO_3H$ (1.1)	68
6	Bu_4NI (1.5)	isoamyl (1.1)	$MeSO_3H$ (1.1)	88
7	Bu_4NI (1.5)	*tert*-butyl (1.5)	$MeSO_3H$ (1.1)	34[a]
8	Bu_4NI (1.5)	isoamyl (1.5)	$MeSO_3H$ (0.1)	< 5
9	Bu_4NI (1.5)	isoamyl (1.5)	$MeSO_3H$ (0.3)	5
10	Bu_4NI (1.5)	isoamyl (1.5)	*p*-TosOH (1.1)	92
11	Bu_4NI (1.5)	isoamyl (1.5)	CF_3CO_2H (1.1)	78

[a] A complex reaction mixture was obtained containing 34% of **2a** as determined by NMR analysis.

reagent for diazonium salt generation. We chose methanesulfonic acid to induce the formation of the diazonium salt from **1a**. The I salt was slowly added as a MeCN solution over 1 hour. In cases where the salt was not perfectly soluble in MeCN a small amount of water was added.

The initial experiment was conducted with NaI as the formal SET and radical-trapping reagent. We were very pleased to find that in situ generation of the aryl diazonium salt is compatible with aryl radical generation, cyclization, and trapping. The targeted cyclized iodide **2a** was isolated in 68% yield (Table 1, entry 1). Yield was further improved by replacing NaI with KI (77%) and CsI (94%, entries 2 and 3) and **2a** was obtained quantitatively when Bu_4NI[8] served as the iodide source (entry 4).[9] Lowering the amount of Bu_4NI and nitrite led to reduced yields (entries 5 and 6). Surprisingly, *t*BuONO did not work well and a complex reaction mixture resulted (entry 7). The use of substoichiometric amounts of $MeSO_3H$ provided a clean reaction but low conversion, showing that a stoichiometric amount of acid is necessary for complete conversion (entries 8 and 9). *p*-Toluenesulfonic acid worked almost as well as $MeSO_3H$; however, with CF_3COOH a lower yield was achieved (entries 10 and 11). The reaction can also be conducted in the presence of air, albeit a slightly lower yield was obtained (86%).

Under optimized conditions (Table 1, entry 4) the scope and limitations of the carboiodination using aryl amines as precursors were investigated (Figure 1). The preparation of all starting arylamines is described in the Supporting Information.

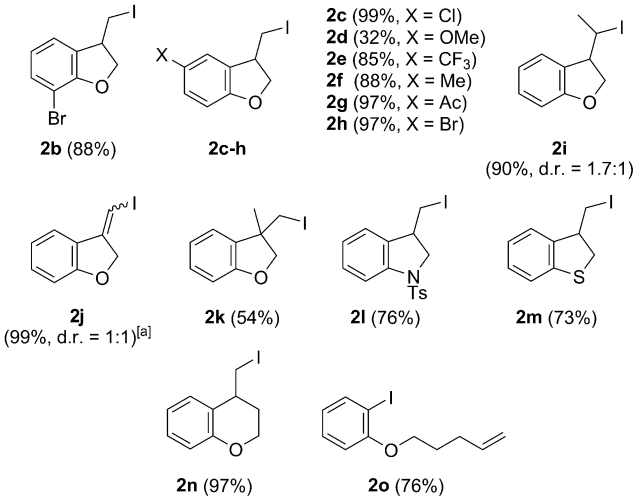
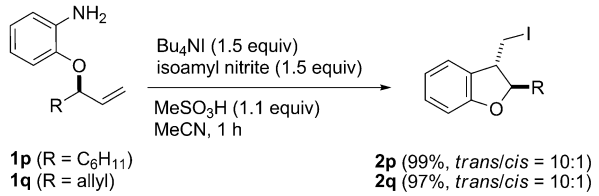


Figure 1. Alkyl iodides **2b–o** obtained by carboiodination of various aryl amines (isolated yields),[a] Yield determined by ^1H NMR spectroscopy using an internal standard due to composition upon isolation.

Halides at the arene ring in the aryl amine are tolerated and iodides **2b**, **2c**, and **2h** were isolated in 88 to 99% yield. CF_3-, methyl-, and acetyl-substituted aryl amines work equally well and the corresponding cyclized dihydrobenzofurans **2e–g** were obtained in very good to excellent yields. However, reaction with the methoxy congener (see **2d**) was not as efficient (32%). As expected, the diastereoselectivity for the exocyclic trapping of the C radical was low and **2i** was isolated in 90% yield as a 1.7:1 diastereoisomer mixture. We found a propargyl phenyl ether to cyclize in quantitative yield as determined by NMR spectroscopy. However, during isolation we realized that product **2j** decomposes upon removal of the solvent.[10] Formation of quaternary C centers is possible as shown by the preparation of **2k** (54%). The corresponding 6-*endo* product was not identified in the crude reaction mixture. Indoline **2l** and benzothiophene **2m** were successfully prepared by application of our novel approach, showing that the method is not restricted to the preparation of O-heterocycles. Pleasingly, an excellent yield was also achieved in the 6-*exo* cyclization and iodide **2n** was isolated in 97% yield. However, 7-*exo* cyclization of the aryl radical cannot compete with direct iodination under the applied conditions: aryl iodide **2o** was obtained in 76% yield and the targeted cyclized product was not identified in the crude reaction mixture.

We next studied the 1,2-stereoinduction in the carboiodination using aryl amine **1p** as the substrate. Iodide **2p** was obtained in quantitative yield with 10:1 *trans*/*cis* diastereoselectivity (Scheme 2). A similar result was obtained in the reaction with aniline **1q**.

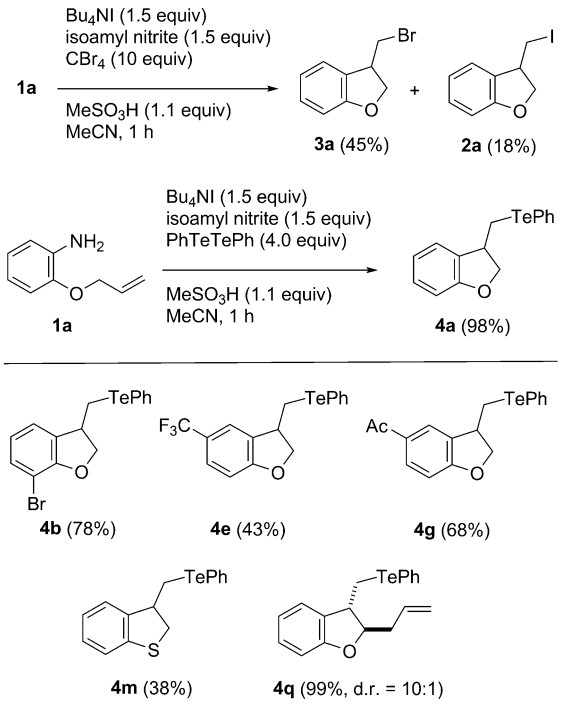


Scheme 2. Diastereoselective carboiodination.

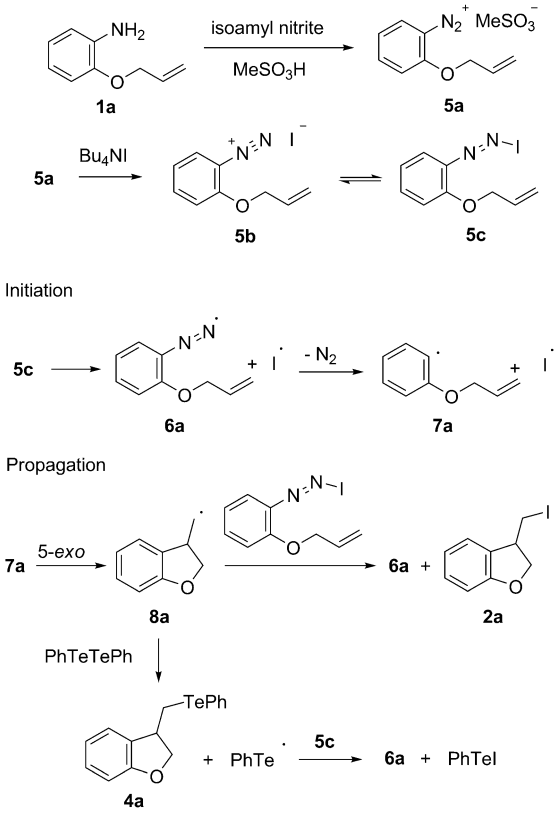
We also investigated whether the intermediate cyclized radicals can be trapped by fast non-I-based radical-trapping reagents. Experiments were mainly conducted with **1a**. Bu_4NI was replaced by Bu_4NBr and Bu_4NCl; however, the corresponding carbobromination and carbochlorination products were not formed. The diazonium salt derived from **1a** did not react with these halide sources.

Therefore, we continued to use Bu_4NI (1.5 equiv) for the clean generation of aryl radicals and added other typical C radical trapping reagents. Neither **2a** nor the carbobromination product **3a** was identified in the presence of *N*-bromosuccinimide (10 equiv). However, adding CBr_4 (10 equiv) under otherwise identical conditions gave the targeted bromide **3a** in 45% yield along with iodide **2a** in 18% yield (Scheme 3). Consequently, we increased the amount of CBr_4 to 30 equiv and obtained **3a** and **2a** in a 7:1 ratio. Unfortunately, combined yield decreased to 35% under these conditions. We therefore switched to other efficient alkyl-radical-trapping reagents and noted that in the presence of PhSeSePh (4 equiv) the carboiodination product **2a** was formed exclusively (50%).

PhTeTePh is known to be a highly efficient alkyl-radical-trapping reagent.[11] Indeed, after some optimization we found that when 4 equiv of PhTeTePh was added the



Scheme 3. Carbobromination and carbotelluration.



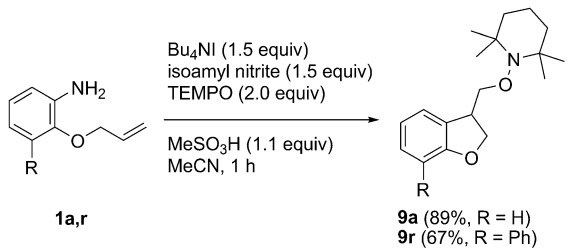
Scheme 4. Suggested mechanism.

telluration product **4a** was obtained in excellent yield (98%). Other carbotelluration products **4b**, **4e**, and **4g** were successfully prepared in moderate to excellent yields (43–78%) with this method. We found that in some cases the reaction works better with 2 equiv of PhTeTePh (see the Supporting Information). As expected based on our results reported above, high stereoselectivity was achieved for the cyclization of aniline **1q** to give the tellurated benzofuran **4q** in quantitative yield. The benzodihydrothiophene **4m** could be successfully prepared with this method, albeit in lower yield.

The suggested mechanism for the radical carboiodination and carbotelluration exemplified with substrate **1a** is presented in Scheme 4. Arylamine **1a** is first transformed with isoamyl nitrite in the presence of $MeSO_3H$ to the diazonium salt **5a**. Exchange of the anion in **5a** with the anion of Bu_4NI provides diazonium iodide **5b**. A literature search revealed only a single X-ray structure of an aryldiazonium iodide, indicating an interaction of the iodide anion with the terminal N atom of the diazonium group (Scheme 4).[12] We therefore assume that the iododiazonium salt **5b** is in equilibrium with its *N*-iododiazene form **5c**. Considering structure **5c**, initiation may occur by N–I homolysis to form I· radical and radical **6a** which undergoes fast N_2 fragmentation to generate the aryl radical **7a**. Alternatively, SET from the iodide to the diazonium cation also leads to **6a**. 5-*exo* cyclization of **7a** generates the alkyl radical **8a** which likely abstracts an iodine atom from aryl-N=N-I (**5c**) to eventually give product **2a** and the chain-carrying **6a**. This I-atom-transfer step must be very fast and can only be suppressed with highly efficient radical-trapping reagents. Moreover, successful trapping of **8a** with external reagents such as CBr_4 and PhTeTePh shows that the trapping of **8a** in the solvent cage with the I· radical formed during initiation is not occurring. The I· radical can dimerize to I_2 which can also act as an alkyl-radical-trapping reagent. However, considering the low concentration of I_2 we currently disfavor I_2 or its adduct with an iodide anion (I_3^-) as the trapping reagents. In the carbotelluration, cyclized radical **8a** is trapped by PhTeTePh to give tellurated product **4a**. The chain is likely sustained by I abstraction of the PhTe· radical from **5c**.

Finally, as an additional efficient radical-trapping reagent, we tested TEMPO in the I-induced cyclization reaction.[13] Pleasingly, with 2 equiv of TEMPO under otherwise identical conditions TEMPO adduct **9a** was isolated in 89% yield starting with aniline **1a** (Scheme 5).[14–16] In analogy, alkoxyamine **9r** was successfully prepared.

In summary, we introduced highly efficient and practical radical carboiodination reactions using aryl amines as substrates. Aryl amines are transformed in situ to the corresponding aryl diazonium salts which in turn act as aryl-radical



Scheme 5. Cyclizing carboaminoxylation.

precursors. Aryl radicals undergo typical 5-*exo* and 6-*exo* cyclization reactions and the cyclized alkyl radicals are then iodinated in a chain reaction. In the presence of PhTeTePh and TEMPO the cyclized radicals are efficiently trapped to provide the corresponding carbotelluration and carboaminoxylation products, respectively. Experiments are very easy to conduct and products are obtained in good to excellent yields.

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[1] a) U. Jahn, *Top. Curr. Chem.* **2012**, *320*, 363 – 369; b) S. G. Newman, M. Lautens, *J. Am. Chem. Soc.* **2011**, *133*, 1778; c) H. Liu, C. Li, D. Qiu, X. Tong, *J. Am. Chem. Soc.* **2011**, *133*, 6187; d) S. G. Newman, J. K. Howell, N. Nicolaus, M. Lautens, *J. Am. Chem. Soc.* **2011**, *133*, 14916; e) D. A. Petrone, H. A. Malik, A. Clemenceau, M. Lautens, *Org. Lett.* **2012**, *14*, 4806. See also: B. M. Monks, S. P. Cook, *Angew. Chem.* **2013**, *125*, 14464; *Angew. Chem. Int. Ed.* **2013**, *52*, 14214.

[2] Y. Lan, P. Liu, S. G. Newman, M. Lautens, K. N. Houk, *Chem. Sci.* **2012**, *3*, 1987.

[3] a) M. R. Heinrich, *Chem. Eur. J.* **2009**, *15*, 820; b) F. Mo, G. Dong, Y. Zhang, J. Wang, *Org. Biomol. Chem.* **2013**, *11*, 1582; c) D. P. Hari, B. König, *Angew. Chem.* **2013**, *125*, 4832; *Angew. Chem. Int. Ed.* **2013**, *52*, 4734.

[4] a) J. A. Murphy, S. J. Roome, *J. Chem. Soc. Perkin Trans. 1* **1995**, 1349; b) J. A. Murphy, *Pure Appl. Chem.* **2000**, *72*, 1327; c) M. Hartmann, Y. Li, A. Studer, *J. Am. Chem. Soc.* **2012**, *134*, 16516; d) H. Jasch, Y. Landais, M. R. Heinrich, *Chem. Eur. J.* **2013**, *19*, 8411.

[5] A. L. J. Beckwith, G. F. Meijs, *J. Org. Chem.* **1987**, *52*, 1922.

[6] a) D. Qiu, L. Jin, Z. Zheng, H. Meng, F. Mo, X. Wang, Y. Zhang, J. Wang, *J. Org. Chem.* **2013**, *78*, 1923; b) D. Qiu, H. Meng, L. Jin, S. Wang, S. Tang, X. Wang, F. Mo, Y. Zhang, J. Wang, *Angew. Chem.* **2013**, *125*, 11795; *Angew. Chem. Int. Ed.* **2013**, *52*, 11581. See also: c) X. Wang, G. D. Cuny, T. Noel, *Angew. Chem.* **2013**, *125*, 8014; *Angew. Chem. Int. Ed.* **2013**, *52*, 7860; d) A. Honraedt, F. Le Callonnec, E. Le Grognec, V. Fernandez, F.-X. Felpin, *J. Org. Chem.* **2013**, *78*, 4604; e) J.-J. Dai, C. Fang, B. Xiao, J. Yi, J. Xu, Z.-J. Liu, X. Lu, L. Liu, Y. Fu, *J. Am. Chem. Soc.* **2013**, *135*, 8436; f) X. Wang, Y. Xu, F. Mo, G. Ji, D. Qiu, J. Feng, Y. Ye, S. Zhang, Y. Zhang, J. Wang, *J. Am. Chem. Soc.* **2013**, *135*, 10330; g) F. P. Crisóstomo, T. Martín, R. Carrillo, *Angew. Chem.* **2014**, *126*, 2213; *Angew. Chem. Int. Ed.* **2014**, *53*, 2181.

[7] L. Chaozhong in *Encyclopedia of Radicals in Chemistry, Biology and Materials, Vol. 2* (Eds.: C. Chatgilialoglu, A. Studer), Wiley, Chichester **2012**, p. 943.

[8] P. Finkbeiner, B. J. Nachtsheim, *Synthesis* **2013**, *45*, 979.

[9] We have recently successfully used Bu_4NI as SET reagent to initiate radical chain reactions: a) B. Zhang, C. Mück-Lichtenfeld, C. G. Daniliuc, A. Studer, *Angew. Chem.* **2013**, *125*, 10992; *Angew. Chem. Int. Ed.* **2013**, *52*, 10792; b) B. Zhang, A. Studer, *Org. Lett.* **2014**, *16*, 1216.

[10] **2k** likely isomerizes to 3-iodomethylbenzofuran which readily decomposes.

[11] a) G. Pattenden, *Chem. Soc. Rev.* **1988**, *17*, 361; b) S. Yamago, *Synlett* **2004**, 1875; c) S. Yamago, *Chem. Rev.* **2009**, *109*, 5051; d) A. Nomoto, A. Ogawa, *Organic Selenium and Tellurium Compounds, Vol. 3* (Ed.: Z. Rappoport), Wiley-VCH, Weinheim, **2012**, p. 623.

[12] J. Z. Gougoutas, *J. Am. Chem. Soc.* **1979**, *101*, 5672.

[13] For reviews on TEMPO as radical trapping reagent see: a) L. Tebben, A. Studer, *Angew. Chem.* **2011**, *123*, 5138; *Angew. Chem. Int. Ed.* **2011**, *50*, 5034; b) T. Vogler, A. Studer, *Synthesis* **2008**, 1979.

[14] See also: A. Wetzel, M. Kirchstein, M. R. Heinrich, *Org. Lett.* **2007**, *9*, 3833.

[15] Radical carboaminoxylations, see: a) A. Studer, *Angew. Chem.* **2000**, *112*, 1157; *Angew. Chem. Int. Ed.* **2000**, *39*, 1108; b) C. Wetter, K. Jantos, K. Woithe, A. Studer, *Org. Lett.* **2003**, *5*, 2899; c) C. Wetter, A. Studer, *Chem. Commun.* **2004**, 174; d) A. Studer, *Chem. Soc. Rev.* **2004**, *33*, 267; e) K. Molawi, T. Schulte, K. O. Siegenthaler, C. Wetter, A. Studer, *Chem. Eur. J.* **2005**, *11*, 2335.

[16] Reaction in the absence of TBAI with TEMPO (2 equiv) provided **9a** in 36% yield showing the I^- to be necessary to get high yields. If I^- is added in a catalytic amount (0.1 equiv), **9a** was obtained in 50% revealing that the I^- is not acting as a catalyst. We currently assume that reaction proceeds as non-chain-process via **5c** which undergoes I-transfer to TEMPO to provide $TEMPO^+/I^-$ and **6a**. $TEMPO^+/I^-$ is an unknown compound which may show similar reactivity as other TEMPO-oxoammonium salts.

