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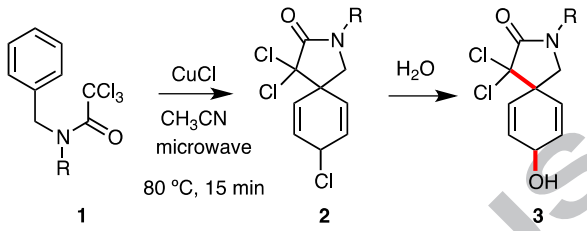

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Dearomative radical spirocyclization from *N*-benzyltrichloroacetamides revisited using a copper(I)-mediated atom transfer reaction leading to 2-azaspiro[4.5]decanes

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ABSTRACT

An atom transfer radical dearomatizing spirocyclization from *N*-benzyltrichloroacetamides using CuCl regioselectively leads to 2-azaspiro[4.5]decadienes, in which the labile allylic chlorine atom is easily replaced by a hydroxyl group in aqueous medium or by quenching with methanol or allylamine. After oxidation of the target compound, the *N*-tert-butyl group can be removed from the resulting spirocyclohexanedione.

Spirocyclic structures are prevalent in a variety of natural products.[1] Among them, the 2-azaspiro[4.5]decane ring system is found embedded in a small number of compounds of diverse biogenetic origin, such as annosqualine,[2] the fungal metabolites triticones[3] and spirostaphylotricins,[4] and some stereoidal alkaloids.[5] Additionally, several synthetic compounds embodying this framework exhibit a wide range of biological activities, including antiangiogenic (e.g. atiprimod),[6] antigastrin,[7] and antiarthritic,[8] as well as HIV-1 protease inhibiton[9] (Figure 1).

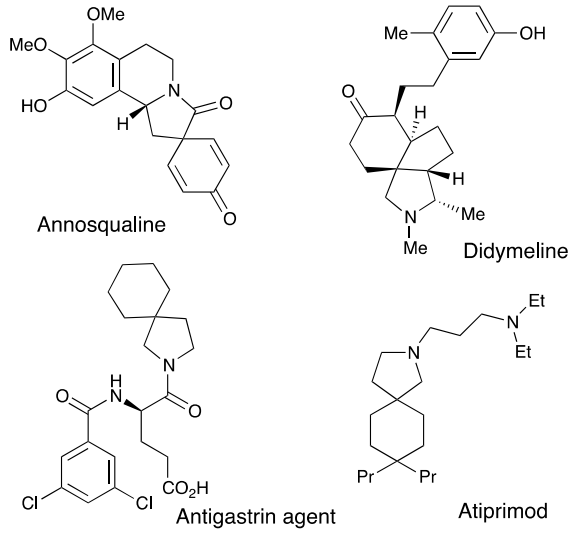

Figure 1. Structures of 2-azaspiro[4.5]decane natural and unnatural products.

2-Azaspiro[4.5]decanes are generally prepared from cyclohexylmethylamine starting materials[10,11] or through a dearomatizing process as the key step from benzene derivatives. In the latter approach, the typical method to construct the spirocyclic core involves oxidative spirocyclization of phenol

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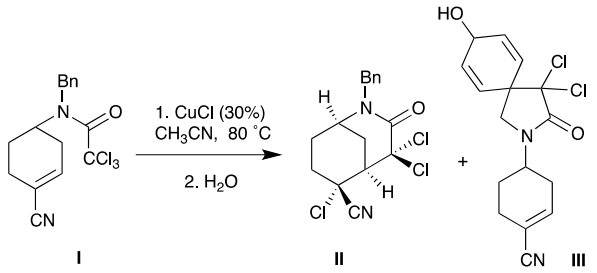
derivatives,[12,13] while there are limited examples of the use of non-activated benzene substrates that could deliver spirocyclohexadienes through a dearomatiszation.[14]

We have recently been interested in copper(I)-mediated atom transfer radical cyclisation (ATRC)[15] of trichloroacetamides leading to six-membered ring formation.[16] During the course of these studies, we disclosed a copper-catalysed ATRC leading to an azaspirocyclohexadienol as a by-product (less than 10%) from trichloroacetamide **I** (Scheme 1).

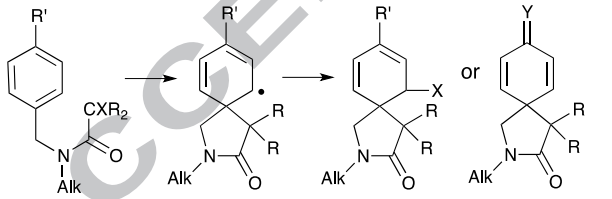


Scheme 1. Radical cyclization of trichloroacetamide **I**.

Inspired by this unprecedented Cu(I)-catalysed spirocyclization, we went on to explore other ways of constructing spirocycles. In this paper we report the first dearomative spirocyclization of benzyltrichloroacetamides mediated by Cu(I) leading to 2-azaspiro[4.5]decane compounds through an ATRC process.[17]

The only precedents for dearomative spirocyclization leading to 2-azaspirodecadienes via a radical process are the following: (i) When working with benzyl derivatives as starting material, the use of Ni-AcOH leads to 1,2-cyclohexadienes, *p*-tolyl compounds lead to a mixture of cyclohexadienes, while adding $(PhSe)_2$ to the reaction medium to trap the cyclohexadienyl radical intermediate regioselectivity provides 1,4-cyclohexadienes.[14] (ii) Using phenol derivatives as substrates in an oxidative process from xanthates, which is initiated and terminated by dilauryl peroxide, provides spirocyclohexanediones[13] (Table 1).

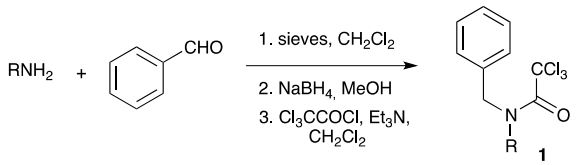
Table 1. Dearomative radical spirocyclization



Promoter	ref	X	R	R´	X/R´ or	Y
Ni-AcOH	14	Cl	Cl	H	Cl/H	H, SePh[a]
$(RO)_2$	13	SC(S)OEt	H	OMe	---	O
CuCl	This work	Cl	Cl	H	---	H, Cl

[a] If $(PhSe)_2$ was added to the reaction mixture.

The trichloroacetamides **1**(a-e)[18] required for our studies were easily available by reductive amination of the corresponding alkylamine with benzaldehyde and acylation of the resulting secondary amines using trichroacetyl chloride (Scheme 2).

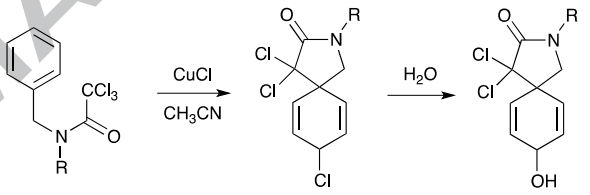


Scheme 2. Synthesis of trichloroacetamides: **1a** (R = Bn, 78%); **1b** (R = Bu, 96%); **1c** (R = *i*Pr (98%); **1d** (R = *c*Hex, 96%); **1e** (R = *t*Bu, 85%).

Initially, we chose trichloroacetamide **1e** as the preferred substrate to develop the methodology, since the bulky *tert*-butyl substituent on the nitrogen atom accelerates radical reactions leading to five-membered rings. This well-established helpful effect is due to the favoring of the productive *Z* rotamer in the proradical haloacetamide.[19]

Using 30 % of CuCl and after 16 h of heating at 80 ºC, we were pleased to see that the main signals in the ^{1}H NMR spectrum of the crude product belonged to a mixture of epimers of spirolactam **2**. However, purification of **2** on silica gel gave a mixture of compounds, showing the instability of the chloro derivatives. Luckily, a simple treatment of the reaction mixture with water at the end of the reaction generated the corresponding alcohols **3**, which were stable enough to be easily separated by chromatography in 65% yield and as a 1.4:1 mixture of epimers (Table 2, entry 1).

Table 2. CuCl-promoted spirocyclization of trichloroacetamides **1**[a]



Entry	R	CuCl [%]	Time	Yield[b] [%]	Ratio[c]
1	*t*Bu (**1e**)	30	16 h[d]	65	1.4:1
2	**1e**	30	15 min	49	3:2
3[e]	**1e**	60	15 min	74	3:2
4	**1e**	60	30 min	68	3:2
5	*c*Hex (**1d**)	60	15 min	29	3:2
6	*i*Pr (**1c**)	60	15 min	42	2:3
7	Bu (**1b**)	60	15 min	17	3:2
8	Bn (**1a**)	60	15 min	24	2:3

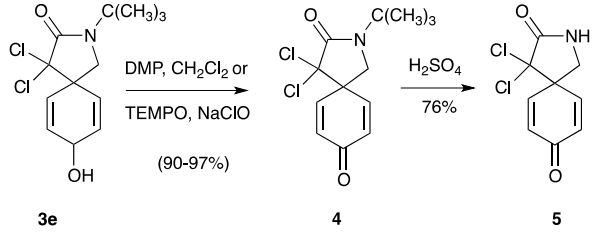
[a] Unless otherwise noted, all reactions were carried out from 200 mg of trichloroacetamide **1** at 80 ºC and using microwave activation. [b] Isolated yield of alcohols **3**. [c] Diastereoisomeric ratio of less and more polar alcohols. [d] Reaction carried out at 80 ºC in a sealed tube. [e] Reaction carried out on a 100 mg scale.

Thus, unlike Zard,[14] who achieved 1,2-dihydrobenzenes by a Ni-AcOH-promoted spirocyclisation,[20] we obtained 1,4-dihydrobenzenes after cyclisation and atom transfer using Cu(I) (Table 1). The sequence involved the generation of the carbamoyldichloromethyl radical, an intramolecular ipso attack on the benzene ring, followed by consecutive regioselective C-Cl bond formation on the initially formed cyclohexadienyl radical.[21] Upon hydrolysis, the lability of the allylic chloride gave the corresponding alcohol **3**. Thus, the overall process constitutes a 1,4-carbooxygenation of the benzene ring present in **1**.

To optimize the process we decided to use microwave activation, but the same catalyst loading, a 15-minute reaction time and further treatment with water gave the same mixture of

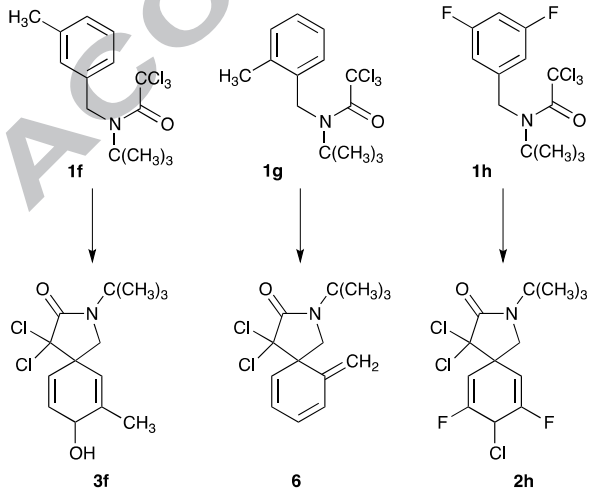
alcohols with a lower yield of 49% (entry 2). The best results were obtained with 60% of CuCl, which gave **3e** in 74% yield (entry 3).[22] Prolonging the reaction time to 30 min did not improve the yield (entry 4).[23] The optimum conditions were then applied to the other trichloroacetamides, and in all cases the corresponding alcohols were obtained in low to moderate yields. As expected, substrates **1a** and **1b**, with non-hindering groups, gave the worst results, whereas isopropyl and cyclohexyl substrates provided alcohols **3** with slightly better yields (Table 2).

The mixture of alcohols **3e** was readily converted to the corresponding ketone **4** in excellent yields using Dess-Martin periodinane or TEMPO. Further cleavage of the *tert*-butyl group in acid medium[24] provided secondary amide **5** in 76% yield (Scheme 3).



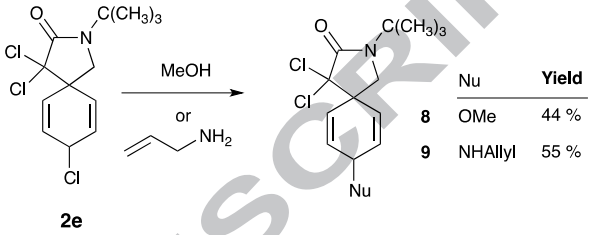
Scheme 3. Synthetic transformations from azaspirolactam **3e**.

We next sought to explore the scope of the reaction and examined a number of substituted benzene derivatives (Scheme 4). Starting materials were prepared following the same reaction sequence of reductive amination and trichloroacetylation as depicted above in Scheme 2. Treatment of 3-methylsubstituted benzene **1f** with CuCl gave a result similar to that observed in the unsubstituted series **1e**, the allylic alcohol **3f** being isolated as a diastereomeric mixture. In contrast, in the 2-methyl substituted benzene **1g**, the trapping of the cyclohexadienyl radical seems to have occurred at C-2, and the chloride derivative evolved to exocyclic methylene derivative **6** through an elimination process. Moreover, for steric reasons the spirocyclization was disfavoured with respect to the ortho-unsubstituted derivatives (**1e**, **1f**), and a remarkable increase in the de-*tert*-butylation reaction from **1g** occurred leading to secondary amide **7** in 25% yield (not shown; see supplementary material). The 3,5-difluorobenzyl derivative **1h** behaved in a particular way, since after the ATRC cyclization the allyl chloride showed a low reactivity in the aqueous medium, and the initially formed chloride **2h,** remaining unchanged, was isolated.



Scheme 4. Substrate scope of the ATRC. Reagents and conditions: CuCl (60%), CH_3CN, μW, 80 ºC, 15 min. Compounds **3f** (54%); **6** (21%); **2h** (42%).

Finally, we used trapping reagents other than water for the allylic chlorides formed after the ATRC, starting from **1e** as the radical precursor (Scheme 5). Thus, when MeOH was added to the reaction in the work-up, a mixture of ethers **8** was isolated. These were noted to be sensitive to the oxygen atmosphere since substantial amounts of ketone **4** were formed on standing in air. Otherwise, when the reaction mixture containing **2e** was treated with allylamine, an epimeric mixture of dienylallylamine epimers **9** was isolated.



Scheme 5. Trapping of chloride **2e** with MeOH or allylamine.

In summary, we have described the first dearomative spirocyclization promoted by CuCl upon a benzene ring. The results obtained with the different trichloroacetamides used in this work again showed the importance of having a bulky group on the nitrogen to achieve the cyclization process. Oxidation of the epimeric alcohol mixture **3e** to the corresponding ketone and further cleavage of the *tert*-butyl group provided polyfunctionalized 2-azaspiro[4.5]decadienone **5**, which is now under study for use as a building block in the synthesis of natural and unnatural compounds.[25]

Acknowledgments

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Supplementary Material

Experimental and NMR data of all compounds and copies of ^{1}H and ^{13}C NMR spectra can be found, in the online version, at hhttp://.

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22. Reaction procedure: In a 10 mL vessel were placed trichloroacetamide **1e** (100 mg, 0.32 mmol), CuCl (19 mg, 0.19 mmol, 60%) and acetonitrile (1 mL). The stirred reaction mixture was heated at 80 ºC using microwave irradiation for 15 min. After reaching rt, water (1 mL) was added, the mixture was stirred for an additional 1 h, and then extracted with CH_2Cl_2. The organics were dried, concentrated and purified by chromatography (CH_2Cl_2 to CH_2Cl_2/AcOEt 98:2) to give separable alcohols **3**e (70 mg, 74%) in a 3:2 proportion. **Less polar:** IR (NaCl, neat): 3529, 3399, 3284, 3039, 2977, 2934, 2870, 1720, 1478,1399, 1365, 1305, 1246, 1222, 1032, 1010, 895, 872, 829, 775, 739, 681, 582, 525 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, COSY): δ 1.43 (9H, s, CH_3), 1.97 (1H, br s, OH), 3.39 (2H, s, 1-H), 4.66 (1H, br s, 8-H), 5.88 (2H, dq, *J* = 10.4, 2 Hz, 6-H and 10-H), 6.23 (2H, ddt, *J* = 10.4, 3, 2 Hz, 7-H and 9-H); ^{13}C NMR ($CDCl_3$, 100 MHz, HSQC): δ 27.1 (CH_3-^{t}Bu), 48.9 (C-5), 52.3 (C-1), 55.4 (C), 62.3 (C-8), 90.5 (C-4), 125.9 (C-6 and C-10), 133.3 (C-7 and C-9), 165.3 (C-3). HRMS (ESI-TOF): Calcd for $C_{13}H_{18}Cl_2NO_2$ 290.0709 (M^++1). Found 290.0719. **More polar:** IR (NaCl, neat): 3254, 3034, 2972, 2871, 1713, 1474, 1400, 1367, 1306, 1245, 1216, 1015, 923, 885, 777, 741, 694, 682, 563, 516 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.43 (9H, s, CH_3), 1.58 (1H, br s, OH), 3.34 (2H, s, 1-H), 4.52 (1H, br s, 8-H), 5.96 (2H, dq, *J* = 10.4, 1.6 Hz, 6-H and 10-H), 6.24 (2H, ddt, *J* = 10.4, 3.6, 2 Hz, 7-H and 9-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 27.1 (CH_3-^{t}Bu), 48.6 (C-5), 52.7 (C-1), 55.4 (C), 62.1 (C-8), 89.7 (C-4), 126.9 (C-6 and C-10), 132.4 (C-7 and C-9), 165.3 (C-3). HRMS (ESI-TOF): Calcd for $C_{13}H_{18}Cl_2NO_2$ 290.0709 (M^++1). Found 290.0698.
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