Tetrahedron Letters 55 (2014) 2865–2868

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# Simultaneous deprotection–oxidation of cyclic hemiacetals: a fine ending for a Ueno–Stork ATRC to dichloro-γ-lactones

Fabrizio Roncaglia [a,*], Franco Ghelfi [a], Fulvia Felluga [b], Valentina Poppi [a]

[a] Dipartimento di Scienze Chimiche e Geologiche, Università degli Studi di Modena e Reggio Emilia, Via Campi 183, I-41125 Modena, Italy
[b] Dipartimento di Scienze Chimiche e Farmaceutiche, Università degli Studi di Trieste, Via L.Giorgeri 1, I-34127 Trieste, Italy

ARTICLE INFO

*Article history:*
Received 13 February 2014
Revised 18 March 2014
Accepted 19 March 2014
Available online 27 March 2014

*Keywords:*
Radical cyclization
Acetal
Lactone
Copper catalyst
Oxidation

ABSTRACT

Recently we found that a copper catalysed Ueno–Stork cyclization can be a very useful means for the expedient synthesis of dichloro-γ-lactones, but, to take advantage of this step, the method still lacks of an efficient and selective follow-up. This Letter describes our progress in that field, unveiling the use of a supported and recyclable $Cr^{(VI)}$ catalyst for the simultaneous deprotection and oxidation of cyclic dichloro hemiacetals.

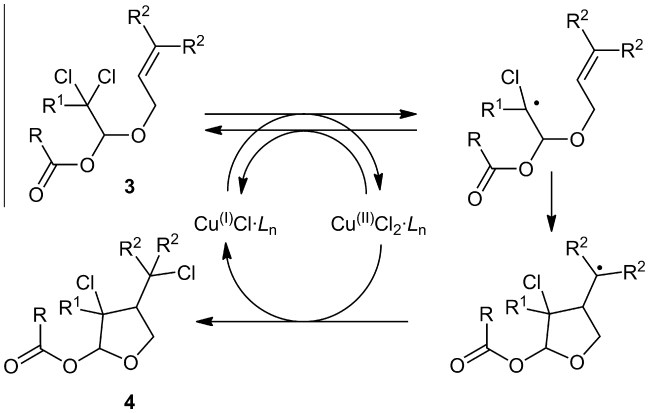


## Introduction

Nowadays, radical methodologies represent useful and valuable tools to build C—C bonds in organic chemistry, frequently employed in the construction of 'small' cyclic molecular structures, that is 5- and 6-membered carbocycles, N-heterocycles or O-heterocycles.[1] Typically these radical cyclizations involve the intramolecular addition of a carbon-centred radical, generated from an organic halide portion, to a tethered unsaturated group.

Compared to other radical cyclization methods, the transition metal catalysed atom transfer radical cyclization (TMC-ATRC) is considerably green and convenient, thanks to: (i) the avoidance of organotin compounds, (ii) the conservation of all the starting C-halogen bonds in the reaction product, (iii) an easier work-up and (iv) a good productivity. The generation and the control of the radical species occur through single electron transfer processes between substrate/radical intermediates and a catalytic redox complex.[2a,b] This one self-assembles in solution when a metal halide (usually $Cu^{(I)}X$) and a nitrogen polydentate organic ligand L (which modulates redox and solubility features) are present. The catalyst first reversibly abstracts an halogen atom, gaining its oxidized state (Scheme 1). Then, acting as a persistent radical,[2c] it irreversibly quenches, by atom transfer, the radical adduct generated in the fast cyclization step. This is the way the catalyst regains its low oxidation state, being ready to start another catalytic cycle.

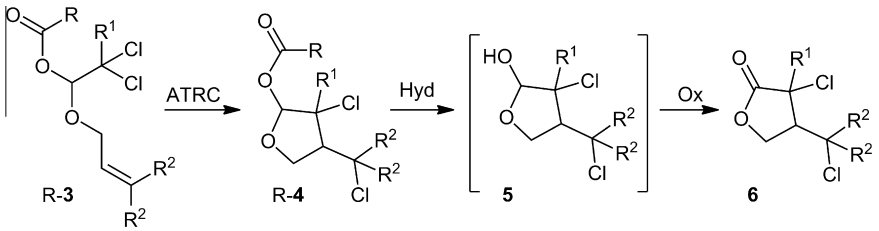
The TMC-ATRC has been largely applied in the cyclization of haloamides to halo-γ-lactams.[3] However, in spite of its clear advantages, its application in other areas was less developed, for example, in the Ueno–Stork reaction. This is an important and versatile method concerning the radical cyclization of α-haloacetals, which is routinely conducted with the standard 'tin hydride' protocol (Giese method).[4a,b] According to this strategy, the difficulties



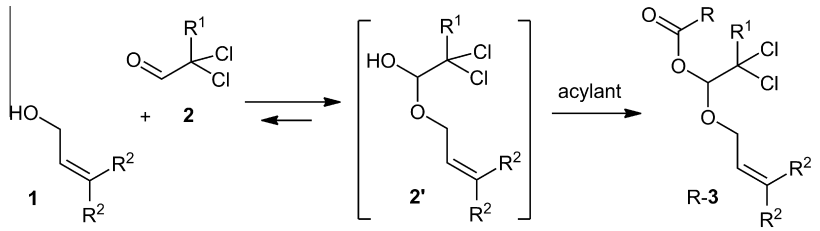

**Scheme 1.** TMC-ATRC of α-haloacetals.

* Corresponding author. Tel.: +39 059 205 5049; fax: +39 059 373543.
*E-mail address:* fabrizio.roncaglia@unimore.it (F. Roncaglia).

http://dx.doi.org/10.1016/j.tetlet.2014.03.090
0040-4039/




**Scheme 2.** TMC-ATRC, hydrolysis and final oxidation towards dichloro-γ-lactones.




**Scheme 3.** Locking the reversible addition of alcohol **1** and aldehyde **2** through the use of a locking auxiliary.

encountered in the construction of γ-lactones through the direct cyclization of α-haloesters, as a result of the high rotational barrier and the low population of the (*E*)-rotamer,[4a,c] are reliably overcome by means of an indirect approach that involves the ring closure of a more flexible α-haloacetal. An oxidation step, by which the ensuing cyclic lactol is converted to the lactone, completes the reaction scheme.

Recently we described an expedient method to obtain dichloro-γ-lactones (**6**, Scheme 2) through a copper catalysed Ueno–Stork ATRC of *O*-allyl-2,2-dichlorohemiacetal acetates **3** (with R = Me) followed by hydrolysis and oxidation of the intermediate cyclic acetals **4**.[5a]

The starting acetal Me-**3** was secured by blocking the hemiacetal **2**′ (Scheme 3) present at the equilibrium in the reversible addition of an allyl alcohol **1** to a 2,2-dichloroaldehyde **2**, with a convenient locking auxiliary, such as the acetyl group.

This method, although new and attractive, requires further improvement, especially regarding: (i) the starting *O*-allyl dichloroacetals (R-**3**) preparation efficiency and (ii) the method employed to convert the ATRC products into the dichloro-γ-lactones.

A sound upgrading of the first point was recently found to be the replacement of the acylating system AcCl/$Et_3N$ with the milder $Ac_2O$/$Et_3N$/DMAP (DMAP = 4-dimethylaminopyridine), effective even with the more critical (sterically crowded) structures.[6] The second desired improvement is the subject of this Letter, where we report our progress towards milder hydrolysis and a fitting oxidation of the intermediate acetals **4**.

## Results and discussion

The choice of a more 'hydrolizable' or labile protecting group for the hemiacetal hydroxyl should strongly favour its final removal, thus we deemed that an alcoxycarbonyl protection could be a good candidate as locking auxiliary.[3,5b] For the best performance, a 'dicarbonate reagent' promises much more selectivity than a 'chloroformate reagent',[6] so the available di-*tert*-butyl dicarbonate ($Boc_2O$) was selected.[8]

Using the same protocol developed for Me-**3**, a series of *O*-allyl-2,2-dichlorohemiacetalcarbonates ($^t$BuO-**3**) was successfully prepared, in comparably good yields (Table 1). These substrates, subjected to CuCl-PMDETA catalysed ATRC, produced the expected

**Table 1**
Preparation of $^t$BuO-**3** (Scheme 3)[a]

| *n*° | Alcohol ($R^2$) | Aldehyde ($R^1$) | Yield (%) | | Yield[b] (%) | |
|---|---|---|---|---|---|---|
| 1 | **1a** (H) | **2a** ($CH_3$) | $^t$BuO-**3a** | 70 | Me-**3a** | 78 |
| 2 | **1b** ($CH_3$) | **2a** ($CH_3$) | $^t$BuO-**3b** | 65 | Me-**3b** | 86 |
| 3 | **1a** (H) | **2b** ($C_3H_7$) | $^t$BuO-**3c** | 75 | Me-**3c** | 82 |
| 4 | **1a** (H) | **2c** ($CH(CH_3)_2$) | $^t$BuO-**3d** | 81 | Me-**3d** | 76 |

[a] **1**(0.1 mol); **2** (0.1 mol); $Et_3N$ (0.11 mol); DMAP(0.01 mol); $CH_2Cl_2$ (35 mL); $Boc_2O$ (0.1 mol).
[b] See Ref. 6.

**Table 2**
ATRC of $^t$BuO-**3**, compared to Me-**3** (Scheme 1)[a]

| *n*° | Product | Yield (%) | Product | Yield[b] (%) |
|---|---|---|---|---|
| 1 | $^t$BuO-**4a** | 90 (15:50:23:12) | Me-**4a** | 84 (13:54:21:12) |
| 2 | $^t$BuO-**4b** | 92 (25:35:27:13) | Me-**4b** | 89 (21:42:25:12) |
| 3 | $^t$BuO-**4c** | 94 (20:46:24:10) | Me-**4c** | 88 (20:46:22:12) |
| 4 | $^t$BuO-**4d** | 91 (23:47:30:0) | Me-**4d** | 93 (22:48:27:3) |

[a] **3** (50 mmol); CuCl (5 mmol); PMDETA (5 mmol); $CH_3CN$ (35 mL); Ar atmosphere; 80 °C, 18 h; yields determined on isolated material. In parentheses the ratio α-*cis*-**4**/α-*trans*-**4**/β-*cis*-**4**/β-*trans*-**4** is shown. Anomeric centres were named according to rule 2-Carb-6 of the IUPAC 'Nomenclature of Carbohydrates (recommendations 1996)'.
[b] Values from Ref. 5a.

series of cyclic carbonates $^t$BuO-**4** in excellent yields (Table 2), indicating that the Boc group does not trouble the cyclization step. As already observed in the ATRC of Me-**3**, the cyclization of $^t$BuO-**3** proceeds under kinetic control with modest diastereoselectivity.

A literature survey regarding the deprotection of the Boc group showed that acid catalysed methods are typical (e.g., trifluoroacetic acid (TFA) in $CH_2Cl_2$ or 4 N HCl in dioxane);[8,9] while the use of basic media is less frequent and unsuitable to work with halogenated substrates.[10] Indeed deprotection with anhydrous HCl in $CH_2Cl_2$ worked effectively with most of $^t$BuO-**4**;[11] but, as expected, the susceptibility of the tertiary exocyclic chlorine atom to acid-catalysed elimination brought $^t$BuO-**4b** to undesired transformation (see later), as observed earlier for Me-**4b**.[5a] Aqueous sulphuric acid or anhydrous silica sulphuric acid easily deprotected $^t$BuO-**4**, but presented the same fault on $^t$BuO-**4b**;[12,13] silica alone wasn't