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# Three-component synthesis of 2-haloalk-2(*Z*)-en-1-ols via tandem haloalkylidenation–aldehyde addition

Rachid Baati,[a] D. K. Barma,[b] J. R. Falck[b,*] and Charles Mioskowski[a,*]

[a]*Université Louis Pasteur de Strasbourg, Faculté de Pharmacie, Laboratoire de Synthèse Bio-Organique (UMR 7514), 67401 Illkirch, France*

[b]*Department of Biochemistry, University of Texas Southwestern Medical Center, Dallas, TX 75390-9038, USA*

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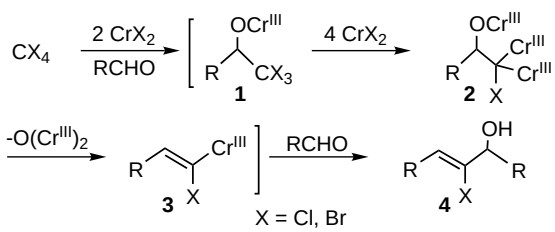
**Abstract**—Cr(II)-induced condensation of $CCl_4$ or $CBr_4$ with an aldehyde stereospecifically generates an (*E*)-α-haloalkylidene chromium carbenoid which adds in situ to a second equivalent of aldehyde furnishing 2-haloalk-2(*Z*)-en-1-ols in high yield.


Organochromium reagents have emerged as versatile synthetic intermediates due in large part to their unique stereo-, regio-, and chemo-selectivities.[1] In particular, alkenylchromiun(III) reagents, most commonly made from alkenyl halides utilizing $CrCl_2$ promoted by nickel salts,[2] have proven useful for the preparation of allyl alcohols under exceptionally mild conditions.[3] In furtherance of these observations, our laboratories reported a broadly applicable and highly stereospecific preparation of (*E*)-chlorovinylidene chromium carbenoids[4] leading to 2-chloropropenyl alcohols,[5] 2-haloalk-2(*Z*)-en-1-ols[6] as well as 1-chloro-1(*Z*)-alkenes and 1-chloro-2-alkoxy-1(*Z*)-alkenes.[7] Herein, we report a three-component condensation involving initial generation of an (*E*)-chlorovinylidene chromium carbenoid (**3**) via Cr(II)-induced addition/condensation of $CCl_4$ or $CBr_4$ with an aldehyde (**1**[8]→**2**) and subsequent in situ vinylation of a second equivalent of aldehyde resulting in 2-haloalk-2(*Z*)-en-1-ols (**4**) (Scheme 1).

The results from subjecting a panel of representative aldehydes to the tandem haloalkylidenation–addition above are summarized in Table 1 and illustrate the generality of the procedure. Simultaneous addition of benzaldehyde (**5**) and $CCl_4$ to a slurry of commercial $CrCl_2$ (Method A) in dry THF furnished the known[9] (*Z*)-Chloroalkenol **6** in excellent yield (entry 1). None of the (*E*)-isomer could be detected by $^1H$ NMR analysis indicating >95% stereochemical purity. Optimal yields required 6 equiv. of $CrCl_2$. This is consistent with two single-electron transfers for each of the oxidative additions of Cr(II) into the three C–Cl bonds (Scheme 1).[10] Yields were lower in most other solvents, inter alia, DMF, $CH_2Cl_2$, $Et_2O$, and $C_6H_6$. Likewise, a catalytic system,[11] using Mn powder to recycle Cr(III) to Cr(II), proved disappointing.

Bromoalkenols are also readily accessible by starting with $CBr_4$ instead of $CCl_4$ and replacing $CrCl_2$ with $CrBr_2$ (conveniently prepared[12] by $LiAlH_4$ reduction of commercial anhydrous $CrBr_3$), e.g., bromide **7**[13] from **5** (entry 2). If $CrCl_2$ is used as the sole reductant in combination with $CBr_4$, one obtains an ~1:1 mixture of **6** and **7**.

Notably, the overall transformation proceeded smoothly with conjugated systems such as cinnamaldehyde (**8**) to give **9** (entry 3) and intramolecularly with benzene-1,2-dicarbaldehyde (**10**) furnishing indene **11**




**Scheme 1.**

*Keywords*: chromium; alkenylation; alcohols; vinylation; stereocontrol.

* Corresponding authors. E-mail: j.falck@utsouthwestern.edu; mioskow@aspirine.u-strasbg.fr

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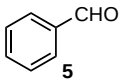
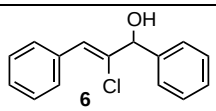
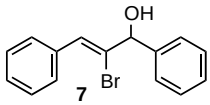
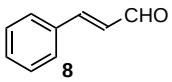
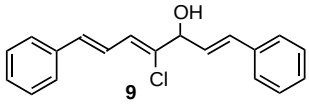
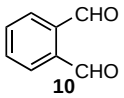
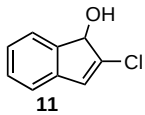
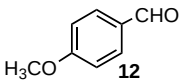
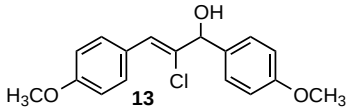
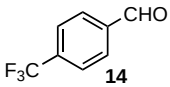
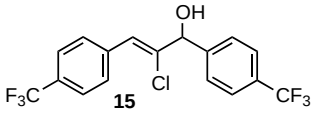
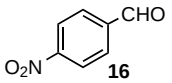
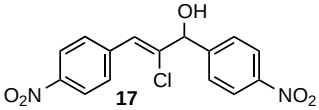
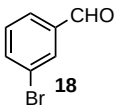
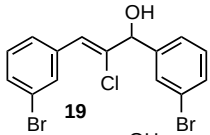
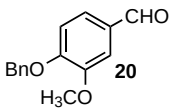
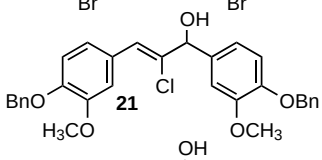
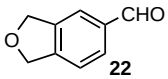
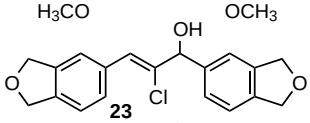
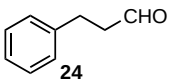
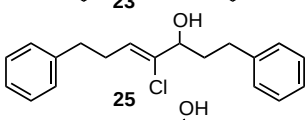
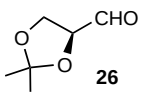
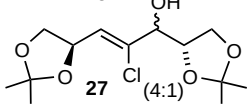
**Table 1.** Tandem synthesis of 2-haloalk-2(*Z*)-en-1-ols

| Entry | Aldehyde | Product | Yield (%) |
|---|---|---|---|
| 1 |  **5** |  **6** | 95 |
| 2 | **5** |  **7** | 65 |
| 3 |  **8** |  **9** | 91 |
| 4 |  **10** |  **11** | 85 |
| 5 |  **12** |  **13** | 94 |
| 6 |  **14** |  **15** | 93 |
| 7 |  **16** |  **17** | 85 |
| 8 |  **18** |  **19** | 93 |
| 9 |  **20** |  **21** | 94 |
| 10 |  **22** |  **23** | 89 |
| 11 |  **24** |  **25** | 85 |
| 12 |  **26** |  **27** (4:1) | 92 |

(entry 4). Neither the reaction rate nor yield were significantly influenced by electron donating or withdrawing substituents, i.e. **12** and **14** gave rise to **13** (entry 5) and **15** (entry 6), respectively, in good yield in 10 h. The compatibility of the general procedure with a variety of common functionality was demonstrated by the conversion of nitro **16** (entry 7), aryl bromide **18** (entry 8), benzyl/methyl diether **20** (entry 9), and bismethyleneoxy ether **22** (entry 10) to **17**, **19**, **21**, and **23**, respectively.

Application of the Barbier-type conditions (Method A) to aliphatic aldehydes was complicated by competitive aldol condensation resulting in depressed yields of chloroalkenol. However, brief pre-incubation of $CCl_4$ with $CrCl_2$ before addition of the aldehyde (Method B) obviated side reactions and restored overall efficiency. For instance, chloroalkenol **25** was efficiently evolved from dihydrocinnamaldehyde (**24**) (entry 11). Even acid sensitive acetonide **26** yielded **27** without incident as a 4:1 mixture of diastereomers (entry 12).

## General procedure

**Method A**: A solution of aldehyde (2 mmol) and $CCl_4$ (1 mmol) in THF (1 mL) was added to a stirring, 0°C suspension of $CrCl_2$ (6 mmol; Strem Chem., 99.9%) in THF (9 mL) under an argon atmosphere. After 10 h at room temperature, the resultant reddish reaction mixture was quenched with water, extracted thrice with ether, and the combined ethereal extracts were evaporated in vacuo. The residue was purified by $SiO_2$ chromatography affording 2-haloalk-2(*Z*)-en-1-ols in the indicated yields (Table 1).

**Method B**: $CCl_4$ (1 mmol) was stirred with a slurry of $CrCl_2$ (6.5 mmol) in dry THF (9 mL) at 0°C under argon. After 15 min, a solution of aldehyde (2 mmol) in THF (1 mL) was added and the stirring was continued at ambient for 10 h. Isolation and purification as described above gave the adduct in the indicated yields (Table 1).

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8. For additional evidence that **1** is an intermediate as well as its utility in the preparation of 'unsymmetrical' chloroalkenols using different aldehydes, see: Baati, R.; Barma, D. K.; Falck, J. R.; Mioskowski, C. *Tetrahedron Lett.* **2002**, *43*, 2183–2185.
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12. (a) Hiyama, T.; Okude, Y.; Kimira, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 561–568; (b) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3179.
13. Spectral data for **7**: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 2.56 (d, 1H, $J=5.1$ Hz), 5.45 (d, 1H, $J=4.2$ Hz), 7.26 (s, 1H), 7.31–7.52 (m, 8H), 7.60–7.70 (m, 2H). Compound **9**: $^1$H NMR $\delta$ 7.45–6.90 (m, 10H), 5.61 (t, 1H, $J=8.0$ Hz), 4.47–4.35 (m, 1H), 2.57 (s, 1H), 2.55–2.35 (m, 6H), 2.20–1.80 (m, 2H); $^{13}$C NMR $\delta$ 144.1, 141.2, 135.1, 131.1, 130.5, 129.1, 128.6, 127.8, 127.1, 123.9, 79.9, 36.1, 34.2, 32.1, 30.4. Compound **13**: $^1$H NMR $\delta$ 7.62 (d, 2H, $J=9.3$ Hz), 7.36 (d, 2H, $J=8.7$ Hz), 6.84–6.92 (m, 5H), 5.33 (d, 1H, $J=4.5$ Hz), 3.79 (s, 3H), 3.78 (s, 3H), 2.64 (d, 1H, $J=5.1$ Hz); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 159.66, 159.51, 133.08, 132.75, 130.95, 128.19, 126.93, 124.69, 114.05, 113.84, 77.91, 55.44. Compound **15**: $^1$H NMR $\delta$ 7.56–7.78 (m, 8H), 7.06 (s, 1H), 5.50 (d, 1H, $J=3.3$ Hz), 2.67 (d, 1H, $J=4.5$ Hz). Compound **17**: $^1$H NMR ($CD_3COCD_3$) $\delta$ 7.44–7.50 (m, 4H), 7.14–7.20 (m, 2H), 7.20–7.07 (m, 2H), 6.60 (s, 1H), 4.29 (s, 2H); $^{13}$C NMR $\delta$ 149.76, 149.05, 148.48, 142.27, 140.17, 131.59, 129.38, 125.30, 124.77, 124.65, 77.75. Compound **19**: $^1$H NMR $\delta$ 7.79 (s, 1H), 7.61 (s, 1H), 7.55 (d, 1H, $J=5.7$ Hz), 7.45 (dd, 2H, $J=6.0$, 10.5 Hz), 7.37 (d, 1H, $J=6.0$ Hz), 7.24 (dd, 2H, $J=5.7$, 11.7 Hz), 6.91 (s, 1H), 5.36 (d, 1H, $J=2.4$ Hz), 2.62 (d, 1H, $J=3.3$ Hz); $^{13}$C NMR $\delta$ 142.3, 136.02, 135.67, 132.28, 131.76, 131.50, 130.36, 130.02, 129.97, 128.13, 125.55, 124.65, 122.94, 122.56, 77.54. Compound **21**: $^1$H NMR $\delta$ 7.26–7.46 (m, 11H), 7.12 (dd, 1H, $J=1.2$, 6.0 Hz), 7.01 (d, 1H, $J=1.2$ Hz), 6.80–6.92 (m, 4H), 5.30 (d, 1H, $J=2.1$ Hz), 5.15 (s, 2H), 5.13 (s, 2H), 3.87 (s, 6H), 2.60 (d, 1H, $J=2.1$ Hz); $^{13}$C NMR $\delta$ 149.80, 149.22, 148.29, 148.28, 137.18, 137.03, 133.59, 133.12, 128.74, 128.71, 128.06, 128.02, 127.54, 127.42, 127.38, 124.94, 122.84, 119.30, 113.74, 113.46, 112.87, 110.53, 78.08, 71.12, 70.98, 56.20, 56.15. Compound **23**: $^1$H NMR $\delta$ 7.33 (d, 1H, $J=1.8$ Hz), 7.05 (dd, 1H, $J=1.8$, 8.1 Hz), 6.89–6.96 (m, 2H), 6.85 (s, 1H), 6.79 (d, 2H, $J=8.1$ Hz), 5.96 (s, 2H), 5.95 (s, 2H), 5.28 (d, 1H, $J=3.3$ Hz), 2.52 (d, 1H, $J=4.5$ Hz); $^{13}$C NMR $\delta$ 148.06, 147.76, 147.71, 147.63, 134.46, 133.13, 128.26, 124.93, 124.42, 120.64, 109.27, 108.37, 108.35, 107.34, 101.41, 101.39, 78.06. Compound **25**: $^1$H NMR $\delta$ 7.51–7.20 (m, 10H), 7.13 (dd, 1H, $J=16$, 10 Hz), 6.81–6.57 (m, 3H), 6.32 (dd, 1H, $J=16$, 6 Hz), 4.97 (t, 1H, $J=6.0$ Hz), 2.22 (d, 1H, $J=6.0$ Hz); $^{13}$C NMR $\delta$ 138.2, 137.8, 136.2, 135.3, 128.7, 128.5, 128.3, 128.1, 127.7, 126.7, 126.5, 126.1, 123.2, 76.1.