

Published in final edited form as:

*Org Lett.* 2009 October 15; 11(20): 4764–4766. doi:10.1021/ol901985c.

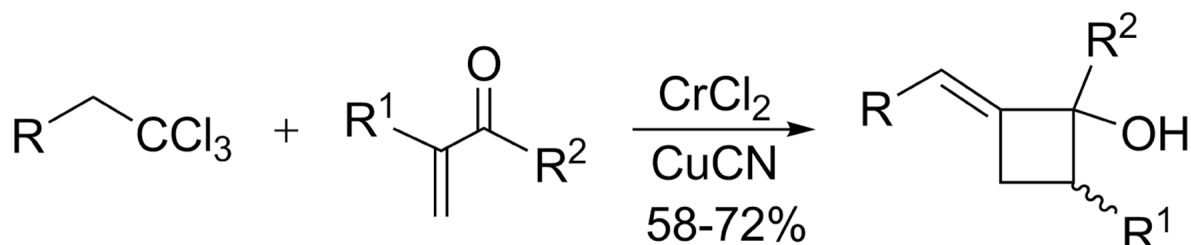
## Cascade Synthesis of (*E*)-2-Alkylidenecyclobutanols

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### Abstract



A facile, one-pot reaction cascade condenses 1,1,1-trichloroalkanes with  $\alpha,\beta$ -unsaturated ketones to unexpectedly furnish moderate to good yields of (*E*)-2-alkylidenecyclobutanols

In recent years, our laboratories<sup>1</sup> and others<sup>2</sup> have introduced an assortment of organochromium reagents and exploited their unique physical/chemical properties for access to a wide range of natural products and high value targets.<sup>3</sup> In continuation of these studies, we sought to extend the utility of select chromium reagents via *in situ* transmetalation and subsequent reaction with electrophiles. In one such example, chromium carbenoid **2** was generated from 1,1,1-trichloroalkane **1** using excess anhydrous CrCl<sub>2</sub>, except both copper cyanide and an  $\alpha,\beta$ -unsaturated ketone **3** were present. We anticipated the (*E*)-vinylchromium (III)-intermediate **2** would undergo transmetalation and subsequent 1,4-conjugate addition with **3**. Unexpectedly, however, (*E*)-2-alkylidenecyclobutanol **4** was isolated as the major product in moderate to good yields (Scheme 1).

Alkylidenecyclobutanols, and the cyclobutanols which are readily derived from them, appear as substructures<sup>4</sup> in many architecturally interesting and/or bioactive natural products.<sup>5</sup> They also display unique reaction manifolds that make them useful as synthetic intermediates.<sup>6</sup> Access to these strained ring systems is generally restricted to [2+2]-cycloadditions,<sup>7</sup> ring expansions or contractions of the corresponding homologs,<sup>8</sup> Wittig<sup>9</sup> and, to a lesser extent, via intramolecular alkylations.<sup>10</sup>

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**Supporting Information Available** Experimental procedures, spectral data of all new compounds, and crystal structure data of **17** (after desilylation) in CIF format. This material is available free of charge via the Internet at <http://pubs.acs.org>.

To better understand the implications of this unusual cascade reaction, we investigated its scope and possible mechanism and report our findings herein. The reaction parameters were systematically optimized using 1,1,1-trichloroalkane **5**,  $\alpha,\beta$ -unsaturated ketone **6**, CrCl<sub>2</sub> (6 equiv) and CuCN (1.2 equiv) as the benchmark system. Yields of **7** were best in THF (Table 1, entry 1), somewhat lower in DME, CH<sub>3</sub>CN and dioxane, and poor in DMF, HMPA, DMSO and EtOAc. The reaction was also highly dependent upon the copper salt. CuCN was superior to all others for producing alkylidenecyclobutanols; little, if any, **7** or conjugate addition was observed with CuI, CuBr, CuCl, PhSCu, or CuTc whereas CuOTf gave a 35% yield of the 1,4-adduct **28**, but no alkylidenecyclobutanol (Scheme 2). Adjuvants, e.g., NiCl<sub>2</sub>, BF<sub>3</sub>·Et<sub>2</sub>O, and KCN were likewise unhelpful as were higher (70 °C) or lower (4 °C) reaction temperatures. The amount of CrCl<sub>2</sub> could be reduced from 6 equiv to 1 equiv using Mn(0) powder as a regeneration agent,<sup>11</sup> although the yield of **7** declined to 24%. Substoichiometric amounts of CuCN also led to significantly lower yields.

Both allylic **8** (entries 2 and 3) and benzylic **12** (entry 4) trichloroalkanes behaved analogously to **5** and afforded adducts **9**, **11**, and **13**, respectively, from ketones **6** and **10**.<sup>12</sup> Importantly, the cascade was compatible with silyl ether **14** (entries 5–8), electron-rich naphthalene **16** (entry 6), and even the aryl bromide **18** (entry 7). X-ray analysis (see Supporting Information) of adduct **17**, following desilylation, confirmed its identity and the *E*-olefinic geometry. The latter was a key insight that must be accommodated by any proposed annulation process (*vide infra*).

It should be noted that benzylic trichloromethylcarbinols, e.g., **20** (entry 8), which are readily prepared from aldehydes, were also suitable precursors for the cascade, albeit with slightly diminished yields of adduct.<sup>13</sup> Addition to  $\alpha$ -substituted  $\alpha,\beta$ -unsaturated ketone **22** proceeded smoothly to furnish **23** as a 1:1.8 diastereomeric mixture (entry 9) and, notably, the polymerization-prone exocyclic ketone **24** was transformed into fused bicyclic **25** (entry 10). In contrast, analogous efforts using the  $\beta$ -substituted analogue **26** (R = Me, Ph) failed to give any **27** (entry 11).

While the mechanistic details remain undefined at present, we speculate that one-electron reduction of enone **3**<sup>14</sup> to enol radical **29** occurs concurrently with the production of  $\alpha$ -halovinylidene chromium carbenoid **2** (Scheme 3).<sup>1j</sup> Subsequent copper mediated Kharasch-type addition<sup>15</sup> and loss of copper chloride from the resultant adduct **30** deliver (*E*)-vinylchromium **31**. Enol quench, perhaps by the previously identified internal proton return process<sup>1j,16</sup> or adventitious water, gives **32** from which **4** is obtained by intramolecular ketone vinylation.<sup>17</sup>

In summary, we have demonstrated a convergent, (*E*)-selective synthesis of 2-alkylidenecyclobutanols based upon mechanistically unique, synergistic chemistry not achievable using either CrCl<sub>2</sub> or CuCN alone.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

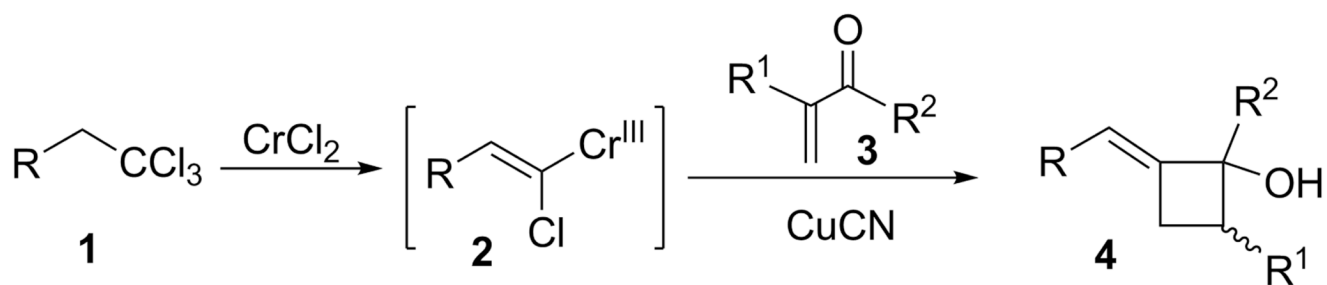
## Acknowledgment

Financial support provided by the Robert A. Welch Foundation and NIH (GM31278). The ANR (Agence National pour la Recherche) is acknowledge for a grant to DK.

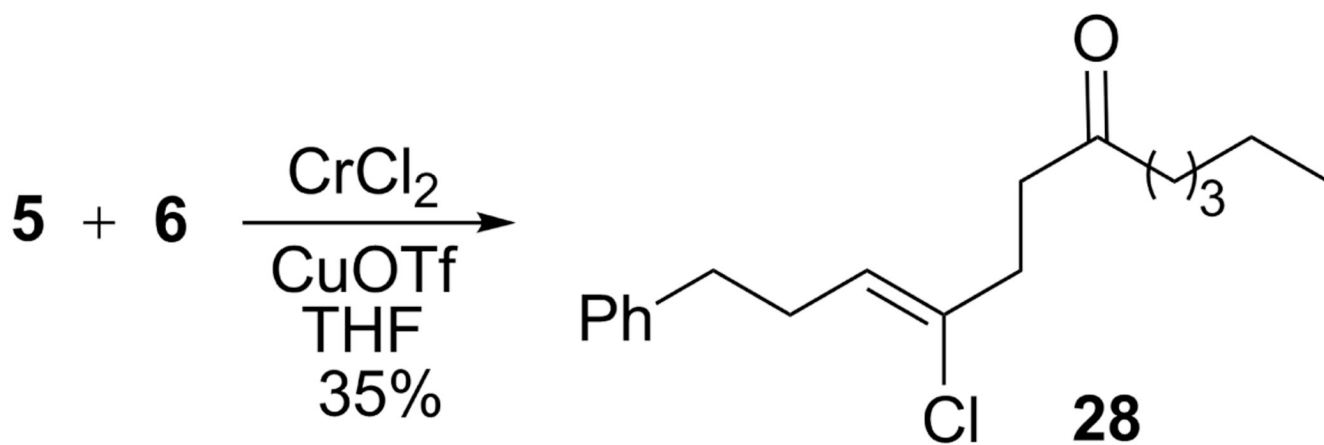
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12. A mixture of 1,1,1-trichloroalkane **1** (0.2 mmol) and  $\alpha,\beta$ -unsaturated ketone **3** (0.24 mmol, 1.2 equiv) in dry tetrahydrofuran (5 mL) was added to a stirring, room temperature suspension of  $\text{CrCl}_2$  (1.2 mmol, 6 equiv; Aldrich Chem. Co.) and  $\text{CuCN}$  (0.24 mmol, 1.2 equiv) in dry tetrahydrofuran (5 mL) under an argon atmosphere. After 12 h, the reaction mixture was quenched with saturated aqueous ammonium oxalate (3 mL) and extracted with  $\text{Et}_2\text{O}$  ( $3 \times 30$  mL). The combined ethereal extracts were washed with water ( $2 \times 40$  mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by  $\text{SiO}_2$ , column chromatography using a gradient of hexane to hexane/ethyl acetate (10:1) affording 2-alkylidenecyclobutanol **4** in the indicated yields (Table 1).
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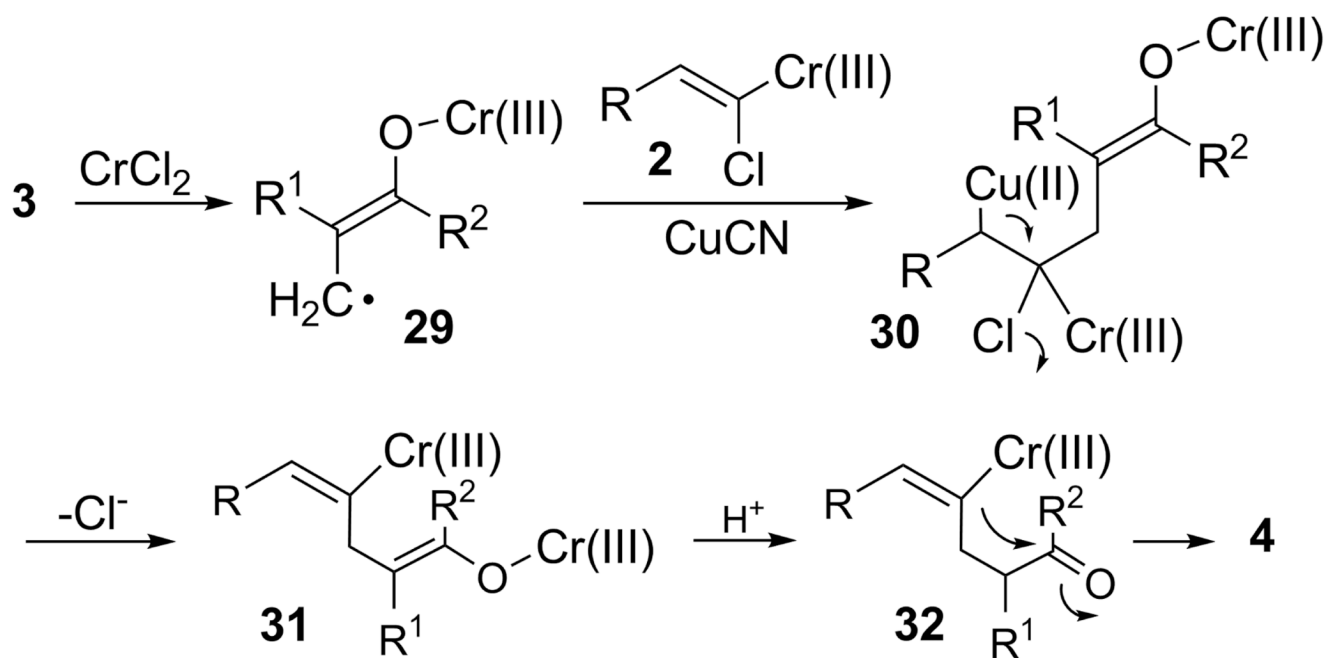
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16. As would be predicted for an internal proton return (IPR) process, there was no change in the yield of **4** if 1.2 equiv of water were intentionally added at the beginning of the reaction. Also, there was no deuterium incorporation into **4** using THF-d<sub>8</sub> as solvent or when the final reaction mixture was quenched with D<sub>2</sub>O. Utilization of 2,2-dideuterated **1** led to **4** fully deuterated at the vinyl but nowhere else in the molecule.
17. Vinyl chromium reagents add to ketones with retention of configuration: Trost BM, Pinkerton AB. *J. Org. Chem* 2001;66:7714. [PubMed: 11701026]



**Scheme 1.**  
Synthesis of (*E*)-2-Alkylidenecyclobutanols



Scheme 2.  
1,4-Conjugate Adduct



**Scheme 3.**  
Proposed Mechanism

**Table 1**  
 Synthesis of (E)-2-Alkylidenecyclobutanols<sup>a</sup>

entry	trichloride	$\alpha,\beta$ -unsat. ketone	adduct	yield (%)
1				64
2				65
3				72
4				65
5				63
6				63
7				64
8				58
9				64 (1:1.8 d.e.)
10				68
11				0

<sup>a</sup> see footnote 12 for general procedure