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

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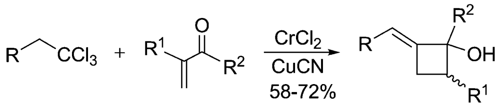
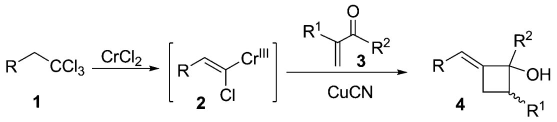
ABSTRACT



A facile, one-pot reaction cascade condenses 1,1,1-trichloroalkanes with α,β-unsaturated ketones to unexpectedly furnish moderate to good yields of (*E*)-2-alkylidenecyclobutanols.

In recent years, our laboratories[1] and others[2] 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.[3] 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 $CrCl_2$, except both copper cyanide and an α,β-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).

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



Alkylidenecyclobutanols, and the cyclobutanols which are readily derived from them, appear as substructures[4] in many architecturally interesting and/or bioactive natural products.[5] They also display unique reaction manifolds that make them useful as synthetic intermediates.[6] Access to these strained

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(1) Review: (a) Baati, R.; Falck, J. R.; Mioskowski, C. *Actualite Chim.* **2009**, *326*, 25. (b) Baati, R.; Mioskowski, C.; Kashinath, D.; Kodepelly, S.; Lu, B.; Falck, J. R. *Tetrahedron Lett.* **2009**, *50*, 402. (c) Bejot, R.; He, A.; Falck, J. R.; Mioskowski, C. *Angew. Chem, Int. Ed.* **2007**, *46*, 1719. (d) Falck, J. R.; Bejot, R.; Barma, D. K.; Bandyopadhyay, A.; Joseph, S.; Mioskowski, C. *J. Org. Chem.* **2006**, *71*, 8178. (e) Falck, J. R.; He, A.; Reddy, L. M.; Kundu, A.; Barma, D. K.; Bandyopadhyay, A.; Kamila, S.; Akella, R.; Bejot, R.; Mioskowski, C. *Org. Lett.* **2006**, *8*, 4645. (f) Baati, R.; Mioskowski, C.; Barma, D.; Kache, R.; Falck, J. R. *Org. Lett.* **2006**, *8*, 2949. (g) Bejot, R.; Tisserand, S.; Reddy, L. M.; Barma, D. K.; Baati, R.; Falck, J. R.; Mioskowski, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 2008. (h) Barma, D. K.; Kundu, A.; Zhang, H.; Mioskowski, C.; Falck, J. R. *J. Am. Chem. Soc.* **2003**, *125*, 3218. (i) Barma, D. K.; Kundu, A.; Baati, R.; Mioskowski, C.; Falck, J. R. *Org. Lett.* **2002**, *4*, 1387. (j) Baati, R.; Barma, D. K.; Falck, J. R.; Mioskowski, C. *J. Am. Chem. Soc.* **2001**, *123*, 9196.

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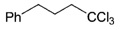
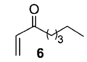
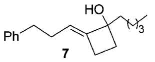
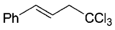
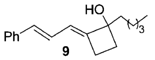
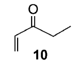
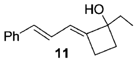
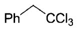
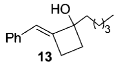
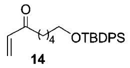
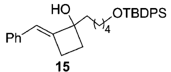
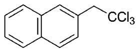
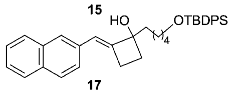
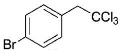
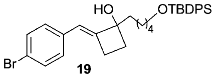
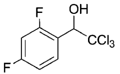
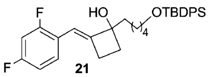
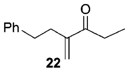
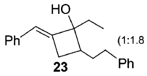
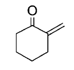
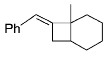
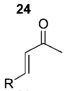
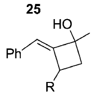
ring systems is generally restricted to [2 + 2]-cycloadditions,[7] ring expansions, or contractions of the corresponding homologues,[8] Wittig[9] and, to a lesser extent, via intramolecular alkylations.[10]

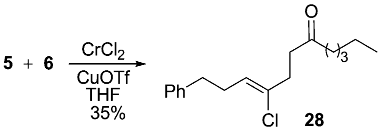
To better understand the implications of this unusual cascade reaction, we investigated its scope and possible mechanism and report our findings herein. The reaction parameters were systematically optimized using 1,1,1-trichloroalkane **5**, α,β-unsaturated ketone **6**, $CrCl_2$ (6 equiv), and CuCN (1.2 equiv) as the benchmark system. Yields of **7** were best in THF (Table 1, entry 1), somewhat lower in DME, CH_3CN, 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., $NiCl_2$, BF_3•Et_2O, and KCN, were likewise unhelpful as were higher (70 °C) or lower (4 °C) reaction temperatures. The amount of $CrCl_2$ could be reduced from 6 equiv to 1 equiv using Mn(0) powder as a regeneration agent,[11] although the yield of **7** declined to 24%. Substoichiometric amounts of CuCN also led to significantly lower yields.

Table 1. Synthesis of (*E*)-2-Alkylidenecyclobutanols[a]

entry	trichloride	α,β-unsat. ketone	adduct	yield (%)
1	 **5**	 **6**	 **7**	64
2	 **8**	**6**	 **9**	65
3	**8**	 **10**	 **11**	72
4	 **12**	**6**	 **13**	65
5	**12**	 **14**	 **15**	63
6	 **16**	**14**	 **17**	63
7	 **18**	**14**	 **19**	64
8	 **20**	**14**	 **21**	58
9	**12**	 **22**	 **23** (1:1.8 d.e.)	64
10	**12**	 **24**	 **25**	68
11	**12**	 **26** (R = Me, Ph)	 **27**	0

[a] See ref 12 for general procedure.

Scheme 2. 1,4-Conjugate Adduct



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**.[12] Importantly, the cascade was compatible with silyl ether **14** (entries 5−8), electron-rich napthalene **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 casacde, albeit with slightly diminished yields of adduct.[13] Addition to α-sub-

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(10) (a) Krohn, K.; Boerner, G. *J. Org. Chem.* **1994**, *59*, 6063. (b) Avila-Zarraga, J. G.; Maldonado, L. A. *Chem. Lett.* **2000**, 512. (c) Other synthetic methodology: Okuma, K.; Kamahori, Y.; Tsubakihara, K.; Yoshihara, K.; Tanaka, Y.; Shioji, K. *J. Org. Chem.* **2002**, *67*, 7355. (d) Mubarak, M. S.; Jennermann, T. R.; Ischay, M.; Peters, D. G. *Eur. J. Org. Chem.* **2007**, *32*, 5346. (e) Barbero, A.; Cuadrado, P.; Garcia, C.; Rincon, J. A.; Pulido, F. J. *J. Org. Chem.* **1998**, *63*, 7531. (f) Bailey, W. F.; Ovaska, T. V. *J. Am. Chem. Soc.* **1993**, *115*, 3080.

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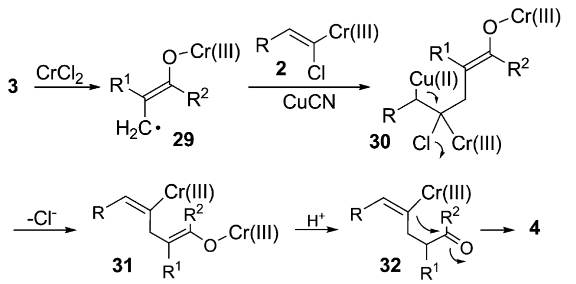
(12) A mixture of 1,1,1-trichloroalkane 1 (0.2 mmol) and α,β-unsaturated ketone **3** (0.24 mmol, 1.2 equiv) in dry tetrahydrofuran (5 mL) was added to a stirring, room temperature suspension of $CrCl_2$ (1.2 mmol, 6 equiv; Aldrich Chem. Co.) and CuCN (0.24 mmol, 1.2 equiv) in dry tetrahydrofuran (5 mL) under an argon atmosphere. After 12 h, the reaction mixture was quenched with saturated aqueous ammonium oxalate (3 mL) and extracted with Et_2O (3 × 30 mL). The combined ethereal extracts were washed with water (2 × 40 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by 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).

stituted α,β-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 β-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**[14] to enol radical **29** occurs concurrently with the production of α-halovinylidene chromium carbenoid **2** (Scheme 3).[1j] Subsequent copper-mediated Kharasch-type addition[15] 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[1j,16] or adventitious water, gives **32** from which **4** is obtained by intramolecular ketone vinylation.[17]

Scheme 3. Proposed Mechanism



In summary, we have demonstrated a convergent, (*E*)-selective synthesis of 2-alkylidenecyclobutanols based upon mechanistically unique, synergistic chemistry not achievable using either $CrCl_2$ or CuCN alone.

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

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.

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[14] Comparable enone Cr(II)-reductions are well precedented: (a) Takai, K.; Morita, R.; Toratsu, C. *Angew. Chem., Int. Ed.* **2001**, *40*, 1116. (b) Toratsu, C.; Fujii, T.; Suzuki, T.; Takai, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 2725. (c) Montgomery, D.; Reynolds, K.; Stevenson, P. *J. Chem. Soc., Chem. Commun.* **1993**, 363.

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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 was intentionally added at the beginning of the reaction. Also, there was no deuterium incorporation into **4** using THF-d_8 as solvent or when the final reaction mixture was quenched with D_2O. 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, B. M.; Pinkerton, A. B. *J. Org. Chem.* **2001**, *66*, 7714.