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Expanding the scope of the Babler–Dauben oxidation: 1,3-oxidative transposition of secondary allylic alcohols

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ABSTRACT

We report the catalytic chromium-mediated oxidation of secondary allylic alcohols to give α,β-unsaturated aldehydes with exclusive (*E*)-stereoselectivity. This facile procedure employs catalytic PCC (5 mol %) and periodic acid (H_5IO_6) as a co-oxidant. This transformation occurs specifically with aromatic substituted allyl alcohols containing both electron withdrawing and electron donating substituents as well as a range of functional groups.

Introduction

α,β-Unsaturated aldehydes are of great importance in several areas of chemical research, ranging from medicinal chemistry through to catalysis and materials science. This moiety is also present in many natural products and the synthetic utility of these compounds is extensive as they can react as excellent electrophiles and Michael acceptors, taking part in a vast array of processes including cycloadditions and nucleophilic reactions.[1]

Since the 1940s chromium(VI)–amine complexes have been used for the oxidation of alcohols.[2a] Typical systems include Jones reagent (CrO_3/aq H_2SO_4), pyridinium dichromate (PDC) and pyridinium chlorochromate (PCC). These reagents have also been used in the oxidation of tertiary allylic alcohols to give α,β-unsaturated carbonyls (1,3-oxidative transposition).[2a–e] This transformation allows strategic modification of a compound's functionality without altering the basic carbon skeleton. Babler and co-workers carried out this process by first forming a tertiary alcohol via alkylation or vinylation of a ketone using Grignard reagents, followed by reaction with PCC to give an α,β-unsaturated system (Scheme 1A).[3] Dauben and co-workers extended the transformation to cyclic systems, thus greatly expanding its utility (Scheme 1B).[4] The method has been used in several total syntheses, notably, that of morphine (Scheme 1C).[5,6] The transformation has also been employed using both oxoammonium salts and IBX as oxidants.[7,8]

Owing to the extraordinarily wide range of possible applications for the enal functionality,[9] it is surprising that so few efforts have been directed at the development of a robust synthetic strategy. The reported synthetic approaches to enals include; the MnO_2 oxidation of cinnamyl alcohols, the Heck coupling of aromatic halides with acrolein or acrylaldehyde diethyl acetal[10] as well as a rhenium-catalyzed Meyer–Schuster rearrangement of propargyl alcohols to aromatic enals.[11] These methods can require the use of expensive transition metal catalytic systems and high temperature/air-free conditions. Deng and co-workers recently developed an organoselenium-catalyzed route to cinnamaldehydes.[12] An iron catalyzed C–H oxidation of allyl arenes to enals has also been reported.[13] Kakiuchi reported a single example of the BnN_3/TsOH induced formation of an aromatic enal from an allylic alcohol in poor yield.[14] Reddy and co-workers reported an acid catalyzed variation of this transformation using a cyano-functionalized vinyl alcohol.[15] Aromatic allyl alcohols are easily accessible from inexpensive and readily available benzaldehydes via reaction with a vinyl Grignard reagent. Herein, we report the first catalytic chromium-mediated 1,3-oxidative transposition of secondary allylic alcohols resulting in the exclusive formation of *trans* α,β-unsaturated aldehydes.

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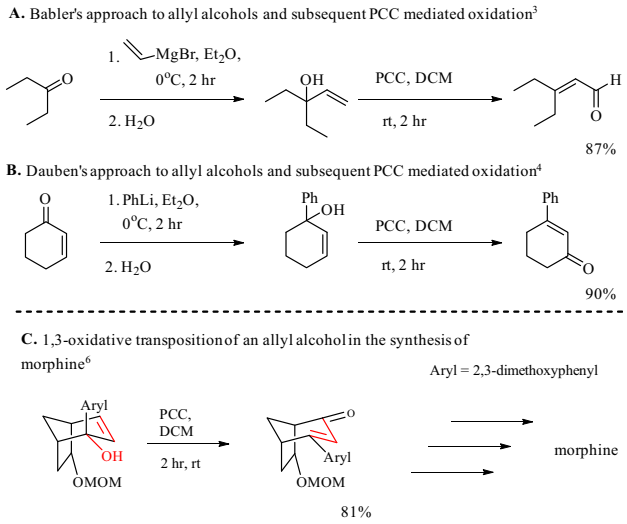
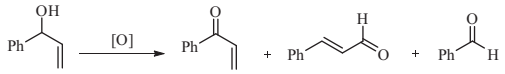


Scheme 1. Previously reported chromium-mediated oxidative transpositions of tertiary allyl alcohols.

Table 1
Preliminary screening of oxidants for the oxidation of phenyl-2-propen-1-ol



1a **1b** **1c** **1d**

Oxidation method	**1b** (%)	**1c** (%)	**1d** (%)
Swern	70	0	0
Dess Martin	81	<5	0
TPAP/NMO	85	0	0
PIFA/TEMPO	42	<5	0
Oxone/TEMPO	38	0	0
NaOCl/TEMPO	56	0	0
PCC	0	71	24
CrO_3/H_2SO_4	80	<5	<5
PDC	51	<5	<5

[a] Detailed reaction procedures are in the ESI.

Results and discussion

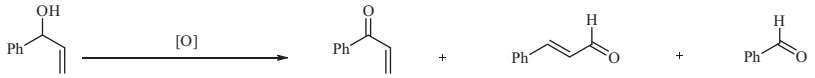
1-Phenyl-2-propen-1-ol (**1a**) was chosen as a test substrate and was easily accessed in excellent yield (95%) from the reaction of vinyl magnesium bromide with benzaldehyde. Table 1 summarizes the results from the oxidant screen.

These oxidants were selected because Cr(VI) and oxoammonium reagents have previously been used for the 1,3-oxidative transposition of tertiary allylic alcohols.[7] Most of the oxidants produced the vinyl ketone product **1b**. The Dess Martin reagent and PIFA/TEMPO system produced only trace amounts of the desired enal **1c**, instead giving the expected vinyl ketone **1b**. There have been reports of PCC induced transposition enal side-products in benzylic and polyaromatic systems.[16,17] Remarkably PCC oxidation of **1a** generated the desired product **1c** in good yield (71%) with no trace of the vinyl ketone **1b**, instead giving only benzaldehyde **1d** (24%) as a side-product. Motivated by this result, attempts were made to optimize the conditions. In an effort to reduce the amount of toxic chromium to catalytic levels we were inspired by the work of Musart[18] and Hunsen,[19] who employed di-*tert*-butyl peroxide (DTBP) and periodic acid (H_5IO_6), respectively, as co-oxidants, allowing the use of catalytic PCC for the oxidation of alcohols to carbonyls.

Table 2 summarizes the optimization of the PCC/co-oxidant system. Initially DTBP was investigated with increasing PCC loading (2.5–10 mol %). Unfortunately vinyl ketone **1b** was the major product with the desired product **1c** present in small quantities. Using H_5IO_6 as the co-oxidant gave **1c** as the major product with benzaldehyde **1d** as a minor impurity. A more detailed screening of PCC loading allowed us to identify 5 mol % as optimum, giving the best yield of 66% with minimum formation of **1d** (15%). A small decrease in yield compared to using stoichiometric PCC (71%) was observed. Increasing the catalytic loading above 5 mol % gave a similar yield but also an increase in side-product **1d**. The process was attempted in the absence of light and under an inert atmosphere with no significant variation in yield.

With the optimized conditions in hand, we then screened a series of substrates (Scheme 2). These compounds were easily prepared from the reaction of the appropriate aromatic aldehyde with vinyl magnesium bromide. A range of molecules with varied functional groups and steric properties were selected. The method is general in terms of functionality with little variation in overall

Table 2
Screening of co-oxidants and PCC loading for the oxidation of **1a**



1a **1b** **1c** **1d**

Co-oxidant	PCC (mol %)	**1b** (%)	**1c** (%)	**1d** (%)
Di-*tert*-butyl peroxide	2.5	23	<5	–
	5	41	12	–
	7.5	52	17	–
	10	50	16	–
Periodic acid	2.5	–	43	11
	3	–	52	17
	4	–	56	14
	5	–	66	15
	6	–	60	21
	7	–	59	26
	7.5	–	53	25
	10	–	61	31

[a] To a flask containing **1a** (5 mmol) and co-oxidant (5 mmol) in MeCN (5 mL) at 0 °C, PCC in MeCN (1 mL) was added dropwise and the reaction monitored by TLC. Product ratios were determined from crude proton NMR.