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Copper-Catalyzed Desymmetrization of Prochiral 4,4-Disubstituted Cyclopentenes *via* a Site-Selective Allylic Oxidation Reaction: A Concise Total Synthesis of Untenone A

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The desymmetrization of prochiral 4,4-disubstituted cyclopentenes *via* a site-selective copper-catalyzed allylic oxidation is described. This study provides a direct comparison to a series of known methods for allylic oxidation, and thus identifies ligand-free copper(I) iodide as the optimal catalyst for this particular process. Notably, this work offers a convenient approach to the preparation of γ -quaternary α , β -unsaturated cyclopentenones, which permits an efficient three-step total synthesis of (±)-untenone A.

The allylic oxidation of alkenes to α , β -unsaturated ketones represents a fundamentally important process in target directed synthesis.¹ Nevertheless, the synthetic utility of this process is often beset with problems associated with poor efficiency and selectivity. Furthermore, the classical methods for allylic oxidation tend to employ toxic, stoichiometric reagents, which seriously detracts from their use in industrial scale applications.^{1,2} Consequently, the development of more environmentally friendly, metalcatalyzed reactions that employ a stoichiometric terminal oxidant has become a subject of increased focus. Although Collman^{3a} reported the first late transition-metal-catalyzed oxidation of cyclohexene to cyclohexenone, the challenges associated with garnering site-selectivity in unsymmetrical systems were delineated by Solomon.^{3b} In light of this challenge, much of the work in this area has focused on symmetrical and/or electronically biased alkenes that furnish excellent selectivity (Scheme 1A). For example, the metal-catalyzed allylic oxidation of cycloalkenes has been reported with rhodium(I/II),³ palladium(II),⁴ manganese(III),⁵ copper(I/II),⁶ cobalt(II)⁷ and bismuth(III),⁸ which afford the

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corresponding α , β -unsaturated ketones in excellent yield and selectivity. Nevertheless, a critical feature with these transformations is the fact that the oxidation does not introduce any stereochemical information. The problem

A. Transition Metal-Catalyzed Allylic Oxidation Reactions – Previous Studies



• M = Rh, Pd, Mn • R = H, Alk, Ar, COR, NO₂ • n = 1, 2, 3



C. Copper-Catalyzed Allylic Oxidation of Prochiral Cyclopentenes – This Work



Scheme 1 Background for the development of the site-selective copper-catalyzed allylic oxidation of prochiral 4,4-disubstituted cyclopentenes.

associated with attaining selective allylic hydrogen abstraction is further manifested by the formation of a fluxional allylic radical intermediate, which can afford constitutional isomers and in certain cases leads to the racemization of the substrate. For example, Baldwin and Swallow provided compelling evidence for the intermediacy

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of an allylic radical in the oxidation of (+)-carvomenthene to (±)-carvotanacetone, which complete undergoes racemization via a prochiral intermediate (Scheme 1B).⁹ We envisioned an alternative scenario in which the allylic oxidation of a prochiral 4,4-disubstituted cyclopentene 1 would permit the construction of γ -quaternary α , β unsaturated cyclopentenones 2 (Scheme 1C). A key and striking feature of this approach is that the initial C-H abstraction is inconsequential, whereas the site-selective trapping of the incipient allylic radical is critical for attaining selectivity. We anticipated that the selective formation of 2a would be possible given the steric bias imparted by the adjacent quaternary in the recombination of the incipient allylic radical. Herein, we now describe the allylic oxidation of prochiral 4,4-disubstituted cyclopentenes 1 with catalytic copper(I) iodide using tert-butyl hydroperoxide as a terminal oxidant to afford the corresponding α,β -unsaturated cyclopentenones 2 in excellent yield (Scheme 1C). Furthermore, we illustrate the synthetic utility with a threestep synthesis of untenone A (4)^{10,11} along with access to an intermediate that was employed in the synthesis of 1,13herbertenediol (5).12

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Table 1 summarizes the preliminary studies on the feasibility of the site-selective allylic oxidation of the

prochiral 4,4-disubstituted cyclopentane 1a using known procedures that have been employed for the ally lie oxidation of cycloalkenes. Although the treatment of methyl 1phenylcyclopent-3-enecarboxylate (1a) with Wilkinson's catalyst in benzene at 70 °C afforded the cyclopentenone 2a in 46% yield with excellent selectivity (entry 1), Rh₂(cap)₄ was both less efficient and selective (entry 1 vs 2). Additional studies probed the utility of Pd(OAc)₂-BINAP and Pd(OH)₂/C, which again furnished **2a** in low yield, but with good selectivity (entry 3 and 4). Similarly, manganese(III) acetate, which had proven to be an excellent catalyst for simple cycloalkenes, provided poor yield albeit excellent selectivity (entry 5). In each case there are significant quantities of unreacted starting material despite the extended reaction times (entry 1-5). In light of the relatively poor efficiency with each of these complexes, we elected to examine cupric and cuprous salts, which had been demonstrated to facilitate the allylic oxidation of alkenes in steroids. Gratifyingly, the allylic oxidation of 1a with catalytic copper(I) iodide furnished 2a in a significantly improved 59% yield and with excellent selectivity (entry 10 vs. 6-9). Further studies probed the impact of the reaction parameters to determine the

Table 1 Op	otimization of the site-selecti	ve copper-catal	yzed allylic oxidati	on of the proch	niral 4,4-disubstitu	uted cyclopenten	e 1a		
		Ph CC	$O_2 Me \xrightarrow{cat. ML_n, {}^{t}BuOOH (TBHP)} base, solvent, temp.$		Ph CO ₂ Me +	Ph CO ₂ Me	3		
entry ^a	metal complex	mol%	base	mol%	solvent	temp (°C)	time (h)	ratio of 2:3 ^b	yield of 2 °
1 ^d	Rh(PPh ₃) ₃ Cl	1	-	-	PhH	70	48	99:1	46
2	Rh ₂ (cap) ₄	1	K ₂ CO ₃	50	CH_2Cl_2	23	24	24:1	29
3 ^e	Pd(OAc) ₂	10	"	25	"	23	24	30:1	22
4	Pd(OH)₂/C	5	"	50	"	"	24	26:1	32
5 ^f	Mn(OAc) ₃ •2H ₂ O	10	_	-	EtOAc	"	48	40:1	18
6	CuCl ₂	5	NaHCO ₃	100	CH₃CN	"	16	26:1	32
7	CuCl	"	"	"	"	"	"	28:1	41
8	CuBr	"	"	"	"	"	"	27:1	25
9	CuCN	"	"	"	"	"	"	28:1	47
10	Cul	"	"	"	"	"	"	34:1	59
11	Cul	5	NaHCO₃	100	CH₃CN	40	36	50:1	82(80) ^g
12	"	"		"	"	60	"	52:1	57

^{*a*} All reactions were carried out on a 0.25 mmol reaction scale using 5 equiv. of TBHP (5.5 M in decane) unless otherwise stated. ^{*b*} Regioselectivity was determined by HPLC analysis of the crude reaction mixtures; **2a** and **3a** are inseparable by column chromatography and **3a** was synthesized *de novo* by the desaturating of the corresponding cyclopentanone. ^{*c*} HPLC yields relative to the internal standard *m*-cresol. ^{*d*} 4.0 equiv. TBHP (5.5 M in decane) was used. ^{*e*} 10 mol% BINAP was added. ^{*f*} 100 mg of 3Å molecular sieves were added. ^{*g*} Isolated yields.

optimal conditions for this transformation. For instance, various inorganic bases were evaluated, which resulted in lower yields of **2a** (NaOAc, K₂CO₃, KHCO₃, Na₂CO₃; SI, Table S1). Furthermore, reducing the amount of base and

increasing the catalyst loading also did not impact the overall efficiency (SI, Table S1). In addition, the examination of various organic solvents, namely, *N*,*N*-dimethylformamide, ethyl acetate, 1,2-dichloroethane, toluene and 1,4-dioxane

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also proved less effective for this transformation relative to

acetonitrile (SI, Table S1). Finally, increasing the reaction temperature to 40 $^{\circ}$ C and extending the reaction time to 36

^{*a*}All reactions were carried out on a 0.25 mmol scale using CuI (5 mol%), 1.0 equiv. NaHCO₃ and 5.0 equiv. of TBHP (5.5 M in decane) in 1.25 mL CH₃CN at 40 °C under air for *ca*. 36 hours. ^{*b*} Regioselectivity was determined by 500 MHz ¹H NMR analysis. ^{*c*} Isolated yields.

Scheme 2. Scope of the copper-catalyzed allylic oxidation of prochiral 4,4-disubstituted cyclopentenes $1\!\!\!\!1^{a,b,c}$

yield and with excellent selectivity (entry 11). Vide Acoustants further increasing the temperature proved detrimental to the efficiency of this process (entry 12). Hence, the ability to employ commercially available copper(I) iodide prompted the examination of the substrate scope for this process.

Scheme 2 outlines the application of the optimized reaction conditions (Table 1, entry 11) to a series of prochiral 4,4-disubstituted cyclopentenes 1. Consequently, cyclopentenes with a 4-methyl ester (CO2Me), tertbutyldimethylsilyl (TBS) protected alcohol or hydroxymethyl pivalate (CH₂OPiv) group in conjunction with either aryl or alkyl substituents were examined, given the potential application of these substituents in target directed synthesis (vide infra). Gratifyingly, the reaction proceeds in a highly efficient and selective manner with both electron-rich and electron-deficient aryl groups (entries 1-9). Additional studies examined the impact of replacing the aryl substituent with alkyl groups, which also results in highly selective oxidation, but with marginally lower efficiency Nevertheless, the reaction is highly (entries 10-18). chemoselective as illustrated by the allyl containing derivatives (entry 16-18), wherein the cyclic olefin is functionalized in preference to the acyclic terminal olefin. Overall, this approach demonstrates excellent scope for the selective oxidation of prochiral 4,4-disubstituted substituted cyclopentenes.

A. Functional Group Manipulations - Iodination and Epoxidation



Reagents and conditions:(a) Hoveyda-Grubbs II (2.5 mol%), CH_2CI_2 , RT, 2 h, *then* DIPEA, TMSOTf, 0°C, 90%; (b) Cul (5 mol%), NaHCO₃ (1.0 equiv.), TBHP (5.0 equiv.), CH_3CN , 40 °C, 36 h, 70%; (c) LDA,NCCO₂Me (2.5 equiv), HMPA/THF (4:1), -78°C to RT, 3 h, *then* HCl, MeOH, RT, 1 h, 65%.

Scheme 3. Functional group manipulations and total synthesis of (±)-untenone A (4)

Scheme 3 outlines the synthetic utility of the γ quaternary α , β -unsaturated cyclopentenones **2** for target directed synthesis. For instance, treatment of

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cyclopentenone 2j with iodine in the presence of DMAP and potassium carbonate, furnished the α -iodo cyclopentenone **6** in 92% yield (Scheme 3A).^{13a} Alternatively, the α -bromo cyclopentenone variant can be readily accessed in analogous yield using a slightly modified protocol (see SI).13b The construction of the α -halo cyclopentenones is particularly important, owing to the fact that they readily participate in metal-mediated cross-coupling reactions.¹⁴ In another synthetic useful demonstration of utility, the cyclopentenone 2d was oxidized using basic hydrogen peroxide to the epoxy ketone 7 in 82% yield and with \geq 19:1 diastereocontrol.¹⁵ The relative configuration of the epoxy ketone 7 was determined via the X-ray crystallographic analysis, which provides an interesting building block for further elaboration.

We envisaged that the copper-catalyzed allylic oxidation could facilitate an expeditious synthesis of the key cyclopentenone core of (\pm) -untenone A (4), which is a natural product that was isolated from the Okinawan marine sponge, plakortis sp. that exhibits modest cytotoxicity against leukemia L1210 cell lines.¹⁰ Ring closing metathesis of the known bis-allyl tertiary alcohol 8,16 prepared via allyl Grignard addition to methyl heptadecanoate, with Hoveyda-Grubbs catalyst followed by in situ trimethylsilyl protection of the tertiary alcohol, furnished the prochiral cyclopentene 9 in 90% overall yield (Scheme 3B). Site-selective coppercatalyzed allylic oxidation of 9 on gram-scale afforded the cyclopentenone 10 in 70% yield with excellent siteselectivity (≥19:1). The synthesis was completed by treating the enolate derived from cyclopentenone 10 with Mander's reagent,¹⁷ followed by acid-mediated desilylation to furnish (\pm) -untenone A (4) in 41% overall yield for the three step sequence to illustrates the utility of this methodology.¹⁸

In summary, we have developed a copper-catalyzed allylic oxidation of prochiral 4,4-disubstituted cyclopenteness for the construction of γ -quaternary α , β -unsaturated cyclopentenones. This study provides a direct comparison of the leading transition-metal-catalyzed allylic oxidation methods and demonstrates a rare example of a highly site-selective allylic oxidation. Finally, the synthetic utility of this method was demonstrated in a three-step total synthesis of (±)-untenone A (4). Overall, this process represents a mild and efficient method for the construction of γ -quaternary α , β -unsaturated cyclopentenones.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

⁺Crystal structure data for **7**: $C_{14}H_{14}O_5$, M = 262.25, colourless, plate-like, $0.199 \times 0.181 \times 0.120 \text{ mm}^3$, monoclinic, space group

P2₁/c(No. 14), *a* = 7.5934(2)Å, *b* = 6.2414(2)Å, *c* = 26.6906(7)Å, *α* = $\gamma = 90^{\circ}$, $\beta = 94.3100(10)^{\circ}$, *V* = 1261.38(6)Å³₃, $\alpha_{1,3}$, $\beta_{2,3,3}$, $\beta_{2,3$

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