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LETTERS

CONVENIENT WACKER OXIDATIONS WITH SUBSTOICHIOMETRIC CUPRIC ACETATE

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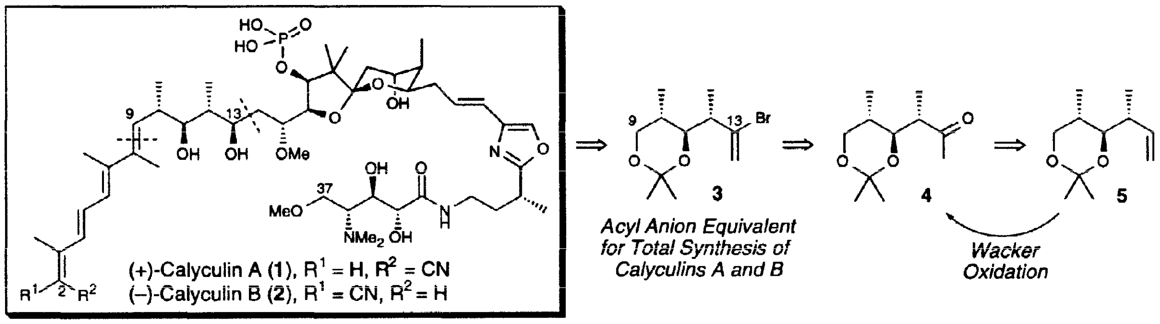
Abstract: A modification of the Wacker oxidation of terminal olefins to methyl ketones using substoichiometric amounts of $Cu(OAc)_2$ as a redox shuttle reagent is described. The modified procedure is generally high yielding despite reduced levels of copper salt and convenient. Importantly, in a problematic case, the conditions suppressed acidic hydrolysis during oxidation of substrate (+)-**5** containing an acetonide. © 1998 Elsevier Science Ltd. All rights reserved.

The palladium-catalyzed Wacker oxidation of terminal olefins to methyl ketones occupies a prominent position among methods for synthesis of natural products.[1] The importance of the transformation derives not only from the numerous methods for introduction of olefinic functionality and the broad utility of methyl ketones, but also from the orthogonal reactivity of these reactants and products. This latter feature renders allyl and vinyl organometallics the synthetic equivalents of acetone enolates and acetyl anions, respectively, upon unmasking by Wacker oxidation. Similarly, alkenyl electrophiles can be utilized as equivalents of various carbonyl compounds.

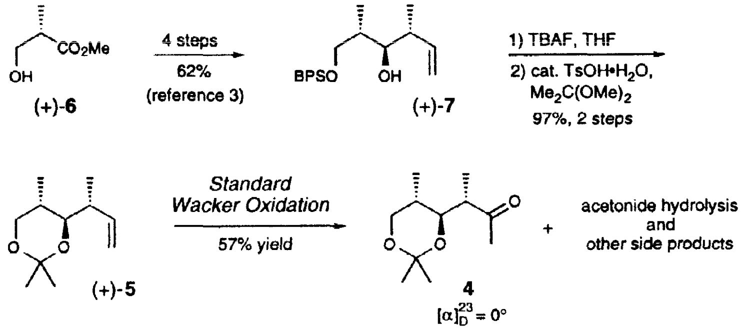
Scheme 1



During our recent total syntheses[2] of the potent and selective marine natural product phosphatase inhibitors calyculins A and B (**1** and **2**, Scheme 1), we required C(9–13) acyl anion equivalent (+)-**3**, which was to be generated via the kinetic enol triflate of methyl ketone **4**. The availability of (+)-**5** via Roush asymmetric crotylboration[3] directed our attention to application of the Wacker oxidation as a means of regiocontrol in the formal overall oxidative bromination of (+)-**5** to vinyl bromide (+)-**3**.

The terminal alkene substrate (+)-**5**[4] was readily obtained in 97% yield from known alcohol (+)-**7**[3] by desilylation and formation of the 1,3-diol acetonide (Scheme 2). To our disappointment, standard Wacker oxidation of (+)-**5** employing the Tsuji *Organic Syntheses* conditions (10 mol %

Scheme 2



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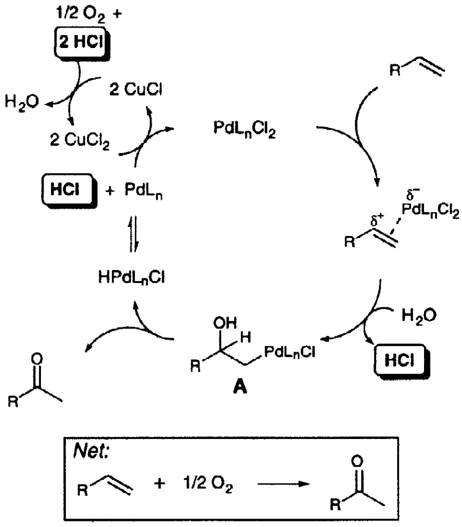
$PdCl_2$, 2 equiv CuCl, O_2, DMF, H_2O)[5] was both sluggish and accompanied by significant acetonide hydrolysis.[6] Although the desired methyl ketone **4** {$[\alpha]^{23}_{D}$ 0° (*c* 2.93, $CHCl_3$)} was obtained, we hoped to suppress acetonide hydrolysis and thereby facilitate large scale material advancement without the necessity of extensive chromatography.

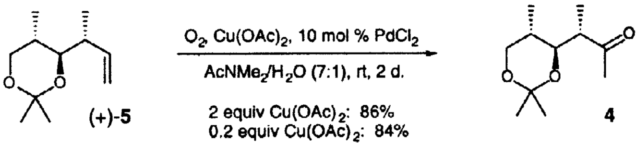
The generally accepted mechanism[1a] for the Wacker oxidation under these conditions (Scheme 3) requires acidic conditions. One equivalent of HCl is extruded during the formation of organopalladium intermediate **A** and a second is formally lost from palladium hydride prior to regeneration of $PdCl_2$ for a new catalytic cycle. The two equivalents of HCl are taken up in the copper redox shuttle, and although net production of HCl is not expected, some transient accumulation of HCl must occur. Not unexpectedly, added base (Na_2CO_3) resulted in no reaction. We reasoned that replacing CuCl with $Cu(OAc)_2$ (i.e., replacing HCl in the catalytic cycle with HOAc) would suppress acidic hydrolysis of **4** while still providing a weak acid to maintain catalytic turnover.[7]

Scheme 3



Modified reaction conditions (Scheme 4) tested the above hypothesis: the alkene (29 mmol) was added with stirring to a mixture of $PdCl_2$ (10 mol %) and $Cu(OAc)_2 \cdot H_2O$ (58 mmol) in $AcNMe_2/H_2O$ (7:1, 57 mL), and the ambient atmosphere was replaced with oxygen. After complete consumption of the alkene (30 h, TLC), pure **4** (86% yield) was obtained following aqueous workup and chromatography. Gratifyingly, no evidence of acetonide hydrolysis was detected (TLC, ^1H NMR).

Scheme 4

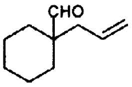
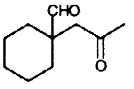
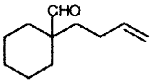
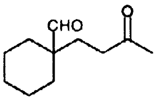
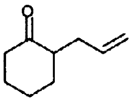
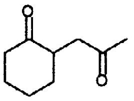
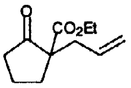
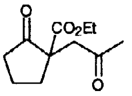
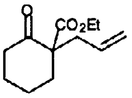
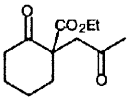
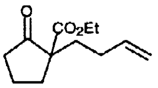
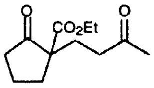


Modified Wacker Oxidation
- substoichiometric $Cu(OAc)_2$
- no acetonide hydrolysis
- improved operational simplicity
- amenable to scaleup

Subsequent experimentation provided further insight. Importantly, utilization of copper could be reduced to a substoichiometric level [20 mol % $Cu(OAc)_2$, 2 d, 84% yield of **4**; Scheme 4]. There are additional operational advantages: since the $Cu(OAc)_2$ redox shuttle begins with Cu(II), preoxidation of the catalyst system by O_2 is not required, unlike CuCl.[8] Because the amount of insoluble material is reduced, reactions are easily stirred, perhaps facilitating oxygen uptake. Removal of soluble $Cu(OAc)_2$ during workup, even in stoichiometric amounts, is trivial. Upon scaleup, the oxidation of alkene (+)-**5** (63 mmol) afforded a similar yield of ketone **4** (82%).

We examined the generality of these conditions (Table 1) by comparing our results with previous literature reports using a variety of functionalized substrates. Yields obtained by our modified procedure (Conditions A) usually exceeded previous results (Conditions B).[1a,5,9] For more appropriate comparison, we also attempted the use of substoichiometric quantities of CuCl (Conditions C), which usually gave similar decreased yields relative to $Cu(OAc)_2$. Thus, $Cu(OAc)_2$ appears more efficient than CuCl using either 20 mol % or 1–2 equiv of copper salts.

Table 1

Entry	Substrate Alkene	Product Methyl Ketone	Conditions,[1] Yield[2] A	B	C
1	(+)-**5**	**4**	84%	57%	-
2	1-decene	2-decanone	87%	73%[3]	66%
3			71%	54%[4]	65%
4			62%	46%[4]	53%
5			75%	68%[5]	69%
6			73%	71%[5]	60%
7			91%	77%[5]	83%
8			87%	61%[5]	75%

(1) Conditions: **A:** O_2, 10 mol % $PdCl_2$, 20 mol % $Cu(OAc)_2$, 7:1 $AcNMe_2/H_2O$, 23 °C. **B:** O_2, 10 mol % $PdCl_2$, 1–2 equiv CuCl, 7:1 DMF/H_2O, 23 °C; preoxidation of Pd/Cu mixture under O_2. For entries 3 and 4, 1.1 equiv benzoquinone was used in place of O_2/CuCl. **C:** O_2, 10 mol % $PdCl_2$, 20 mol % CuCl, 7:1 DMF/H_2O, 23 °C; preoxidation of Pd/Cu mixture under O_2. (2) Yields shown for conditions A and C are either for pure isolated methyl ketones (entries 1–3, 5) or are obtained by ^1H NMR analysis of chromatographed methyl ketones containing 3–10% of isomeric carbonyl compounds. Yields shown for conditions B are obtained from the original literature except for entry 1 (this work). (3) Reference 5. (4) Reference 9. (5) Reference 1a.

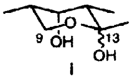
It should be noted that some limitations of the Wacker oxidation were not ameliorated by our modified protocol. Regardless of the conditions, small amounts of isomeric carbonyl compounds (3–10%) were produced in most cases, as is typically observed in the Wacker oxidation.[1] Allylic alcohols and acetates were not cleanly oxidized (Conditions A); low yields and mixtures were obtained (results not shown).[10] Palladium acetate offered no improvement; after two days, less than 30% conversion of 1-decene was observed.

In summary, a convenient, generally applicable modification of the Wacker oxidation using $Cu(OAc)_2$ as a redox shuttle reagent has been described. With these conditions, a problematic acid-sensitive alkene substrate was conveniently oxidized in high yield without complications from acetonide hydrolysis. The modified procedure[11] features substoichiometric utilization of copper and practical advantages in operational simplicity.

Acknowledgments. Support was provided by the National Institutes of Health (National Cancer Institute) through grant CA-19033 and a postdoctoral fellowship to G. K. F.

REFERENCES AND NOTES

1. a) For a review, see: Tsuji, J. *Synthesis* **1984**, 369. b) For an application to synthesis of pseudomonic acid C, see: Balog, A.; Yu, M. S.; Curran, D. P.; Yu, G.; Carcanague, D. R.; Shue, Y.-K. *Synthetic Commun.* **1996**, *26*, 935. c) For an application to synthesis of swinholides, see Paterson, I.; Cumming, J. G.; Smith, J. D.; Ward, R. A.; Yeung, K.-S. *Tetrahedron Lett.* **1994**, *35*, 3405. d) For other recent synthetic applications, see Pellissier, H.; Michellys, P.-Y.; Santelli, M. *Tetrahedron Lett.* **1994**, 35, 6481; Money, T.; Wong, M. K. C.*Tetrahedron* **1996**, 6307.
2. Smith, A. B., III; Friestad, G. K.; Duan, J. J.-W., Barbosa, J.; Hull, K. G.; Iwashima, M.; Qiu, Y.; Spoors, P. G.; Salvatore, B. A. *J. Am. Chem. Soc.*, submitted.
3. Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348.
4. The structure assigned to each new pure compound is in accord with its IR, 500 MHz ^1H and 125 MHz ^{13}C NMR spectra, as well as appropriate parent ion identification by high resolution mass spectrometry.
5. Tsuji, J.; Nagashima, H.; Nemoto, H. *Org. Synth., Coll. Vol. 7* **1990**, 137.
6. The major side product had ^1H NMR properties consistent with hemiketal **i**.



i

7. Cupric acetate has been empoyed in industrial Wacker oxidation, see: Hrusovsky, M.; Vojtko, J.; Cihova, M. *Hung. J. Ind. Chem.* **1974**, *2*, 137; *Chemical Abstracts* **1975**, *82*, 139205.
8. With CuCl as the redox shuttle reagent, a mixture of $PdCl_2$ and CuCl is typically stirred under O_2 for 1–2 h prior to introduction of the alkene substrate. It has been noted that the use of $CuCl_2$ leads to chlorinated byproducts, see reference 1a.
9. Molander, G. A.; Cameron, K. O. *J. Org. Chem.* **1993**, *58*, 5931.
10. Alternate mechanisms may intervene in the oxidations of allylic alcohols and acetates.
11. Representative procedure: A suspension of alkene (+)-**5** (1.84 g, 10.0 mmol), $PdCl_2$ (177 mg, 1.0 mmol), and $Cu(OAc)_2 \cdot H_2O$ (0.40 g, 2.0 mmol) in *N,N*-dimethylacetamide (15 mL) and water (2 mL) was placed under oxygen (1 atm) and stirred for 3 d. The mixture was diluted with ether (10 mL), filtered through Celite employing ether (3 x 10 mL) to wash the filter cake, poured into water (20 mL), and extracted with ether (3 x 5 mL). The organic phase was washed with brine (3 x 10 mL), dried over Na_2SO_4, and concentrated. Adsorption on silica gel and gradient flash chromatography (hexanes → 3:1 hexanes/ethyl acetate) afforded **4** (1.68 g, 84.0% yield).