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One-pot synthesis of α,β-epoxy ketones by palladium-catalyzed epoxidation–oxidation of terminal allylic alcohols

Fateh V. Singh, Jesus M. Pena, Hélio A. Stefani *

Departamento de Farmácia, Faculdade de Ciências Farmacêuticas, Universidade de São Paulo, São Paulo, SP, Brazil

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ABSTRACT

Described herein is a one-pot synthesis of α,β-epoxy ketones using a palladium-catalyzed epoxidation–oxidation sequence. Functionalized terminal allylic alcohols are treated with *m*-CPBA under mild reaction conditions to obtain the α,β-epoxy ketones. The main benefit of this approach is that the epoxidation of the terminal double bond and the oxidation of the secondary alcohol occured in the same reaction under mild reactions and both electron-donating and electron-withdrawing functionalities are tolerated in the reaction sequence.

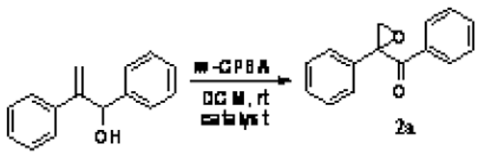
1. Introduction

α,β-Epoxy ketones are key intermediates in the syntheses of several biologically important synthetic and natural products. Recently, aromatic compounds possessing α,β-epoxy ketone cores were used as synthetic intermediates in the synthesis of nitrogen-containing heterocycles that were reported to be potent and selective CB_1 cannabinoid receptor antagonists[1] and novel non-mutagenic antibacterial agents.[2] α,β-Epoxy ketones have also been used as precursors in the synthesis of optically active phenylpropylene oxides.[3] In addition, cyclic epoxy ketones have been identified as key starting materials for the synthesis of functionalized isophosphinoline compounds,[4] chromones[5], and ipriflavones.[6]

However, the synthesis of α,β-epoxy ketones has not been thoroughly examined, and most of the reports on this topic focus on the epoxidation of α,β-unsaturated ketones with peracids. Arylated epoxy ketones can be synthesized by treating 1,2-diarylethane-1,2-diones with dimethyloxosulfonium methylide, but this approach suffers from the formation of side products.[7] In the mid-1980s, Griesbaum and his research group described the synthesis of α,β-epoxy ketones by ozonizing acyclic, conjugated dienes, but this approach also leads to the formation of undesired side products.[8] Epoxy ketone cored architectures have been synthesized by the nucleophilic acylation of chlorocarbonyl compounds, but the products are obtained in low yields.[9] In the past two decades, α,β-epoxy ketones have been synthesized by the epoxidation of chalcones using polyamino acids as catalysts; this reaction involves a triphasic system that consists of an aqueous, basic peroxide, an organic solvent, and an insoluble polyamino acid such as poly-L-leucine.[10] More recently, arylated α,β-epoxy ketones were synthesized by the homologation of vicinal polyketones with diazomethane.[11] Lange et al.[1] reported the synthesis of these chemical entities by using *m*-CPBA to epoxidize chalcones. Cella et al.[12] reported the tetramethylpiperadine–HCl-catalyzed epoxidation–oxidation of endocyclic allylic alcohols by *m*-CPBA.

We previously demonstrated the oxidative cleavage of the terminal double bond in 1,1-diarylethenes using *m*-CPBA as the oxidant.[13] In the context of an ongoing project in our laboratory, we needed to cleave the terminal double bond of 1,2-diarylprop-2-

Table 1
The effects of various catalysts on the epoxidation of 1,2-diphenylprop-2-en-1-ol (**1a**) with *m*-CPBA



1a

Entry	Catalyst[a]	Reaction time (h)	Yield[b] (%)
1	$PdCl_2$	4	81
2	$Fe(acac)_3$	6	69
3	$Cu(OAc)_2$	7	21
4	CuI	10	12
5	$NiCl_2$	8	—
6	$Pd(OAc)_2$	8	57
7	$FeCl_3$	10	16
8	$FeSO_4$	24	—
9	$Pd(PPh_3)_4$	24	—
10	$PdCl_2(dppf)\cdot CH_2Cl_2$	24	35
11	TDBzDP	24	22

[a] 5 mol % of catalyst.
[b] The yields were determined by GC analysis.

* Corresponding author. Tel.: +55 11 818 3654; fax: +55 11 3 815 4418.
E-mail address: hstefani@usp.br (H.A. Stefani).

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Table 2
The effect of solvent on the epoxidation of 1,2-diphenylprop-2-en-1-ol (**1a**) with *m*-CPBA

Entry	Solvent	Reaction time (h)	Yield[a] (%)
1	DCM	4	81
2	MeOH	20	15
3	DMF	24	nr
4	THF	24	nr
5	Toluene	24	Trace
6	1,4-Dioxane	24	nr
7	CCl_4	10	52

[a] The yields were determined by GC analysis.

Table 3
The optimization of equivalents of *m*-CPBA and palladium chloride in the epoxidation of 1,2-diphenylprop-2-en-1-ol (**1a**) with *m*-CPBA

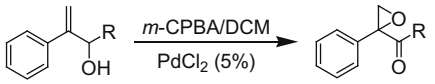
Entry	*m*-CPBA (equiv)	$PdCl_2$ (mol %)	Reaction time (h)	Yield[a] (%)
1	1	5	10	—
2	1.5	5	10	35
3	2.0	5	8	82
4	3.0	5	8	70
5	2.0	2	12	53
6	2.0	5	4	82
7	2.0	8	4	83
8	2.0	10	4	80

[a] The yields were determined by GC analysis.

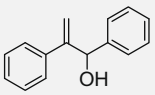
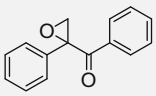
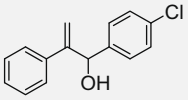
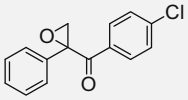
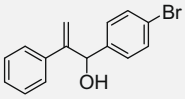
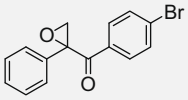
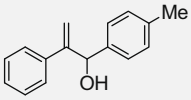
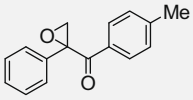
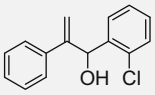
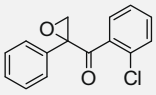
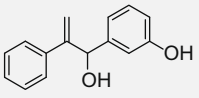
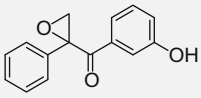
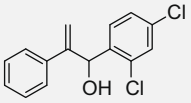
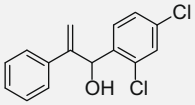
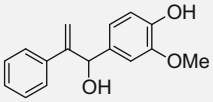
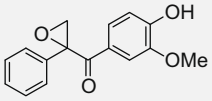
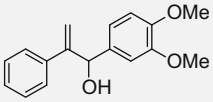
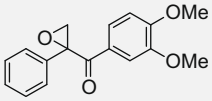
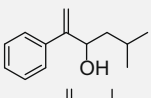
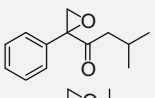
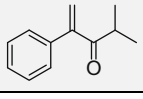
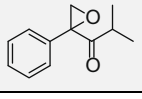
en-1-ol derivatives. In order to identify new approaches for the oxidative cleavage of terminal double bonds, we focused our attention on the reaction between *m*-CPBA and the terminal double bond of allylic alcohols.

Herein, we report a general approach for the one-pot synthesis of α,β-epoxy ketones by the palladium-catalyzed epoxidation–oxidation of functionalized terminal allylic alcohols using *m*-CPBA un-

Table 4
The epoxidation of allylic alcohols **1a**–**k** with *m*-CPBA



1 **2**

Entry	Allylic alcohol (**1**)	Product (**2**)	Reaction time (h)	Yield[a] (%)
a			4	81
b			5	85
c			5	83
d			8	70
e			14	64
f			8	62
g			13	72
h			12	75
i			10	64
j			8	73
k			7	77

[a] Isolated yields.

der mild reaction conditions. The strength of this approach is that the epoxidation of terminal double bond and oxidation of allylic alcohol occurring in the same reaction under mild conditions and permits flexibility of introducing an electron-donating or electron-accepting functionality in epoxy ketone cored aromatic architectures.

Prior to developing new *m*-CPBA-mediated oxidation reactions, we focused on the synthesis of functionalized allylic alcohols. We have synthesized compounds **1a–k** by the nucleophilic addition of (1-phenylvinyl)magnesium bromide to various aldehydes.[14]

After preparing the necessary allylic alcohols, we turned our attention to the *m*-CPBA-mediated epoxidation of the terminal double bonds in allylic alcohols **1a–k**. 1,2-Diphenylprop-2-en-1-ol (**1a**) was chosen as a model substrate, and a variety of conditions were screened (Table 1). The reactions were monitored by TLC or GC.

In order to find an appropriate catalyst for the epoxidation of 1,2-diphenylprop-2-en-1-ol (**1a**), we evaluated several transition metal catalysts. The best result was obtained with $PdCl_2$ (Table 2, entry 1), and the product was formed in 81% yield.

We screened a number of solvents in this epoxidation reaction (Table 2). The best result was achieved with dichloromethane (DCM), and the product was obtained in 81% yield (Table 2, entry 1). In contrast, no product was formed when the reaction was run in DMF, THF, or 1,4-dioxane.

Next, we focused on determining the optimal amount of *m*-CPBA for this epoxidation reaction. We performed the same reaction using 1.0, 1.5, 2.0, and 3.0 equiv of *m*-CPBA (Table 3, entries 1–4), and the maximum yield (82%) of the desired product (**2a**) was observed with 2.0 equiv of *m*-CPBA (entry 3).

The catalyst loadings were also evaluated (Table 3, entries 5–8), and the best yield (83%) was obtained with 8 mol % of $PdCl_2$ (Table 3, entry 7). However, using 5 mol % of $PdCl_2$ provided the product in nearly the same yield (82%) (Table 3, entry 6). As such, all the subsequent experiments employed 5 mol % of $PdCl_2$.

Our next step was to optimize the synthesis of phenyl(2-phenyloxiran-2-yl)methanone (**2a**) from diphenylprop-2-en-1-ol (**1a**) (Table 4). The best conditions were found to include 1.0 equivalent of 1,2-diphenylprop-2-en-1-ol (**1a**), 2.0 equiv of *m*-CPBA, and 5 mol % of $PdCl_2$ in DCM; this mixture was stirred at room temperature under nitrogen for 4 h. Using these optimized conditions, we prepared a series of aryl(2-phenyloxiran-2-yl)methanones (compounds **2a–k**) (see Table 4).[15]

We found that the oxidation reaction was successful with both electron-donating and electron-withdrawing substitutions on the benzene ring, but in general, the products were obtained in better yields when an electron-withdrawing substituent was present. This reaction was also successful with α-alkyl olefinic alcohols **1j** and **1k**.

2. Conclusion

In summary, we have identified a simple and useful approach for synthesizing α,β-epoxy ketones by a palladium-catalyzed epoxidation–oxidation sequence; this process uses functionalized terminal allylic alcohols as substrates and *m*-CPBA as the stoichiometric oxidant. The strength of this approach is that the epoxidation of terminal double bond and oxidation of allylic alcohol occurring during same reaction under mild conditions and permits flexibility of introducing an electron-donating or electron-accepting functionality in epoxy ketone cored aromatic architectures.

Acknowledgments

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14. *General procedure for the synthesis of 1,2-diphenylprop-2-en-1-ol derivatives* **1a–k**: a solution of 1-bromo-1-phenylethylene (10 mmol) in THF (20 mL) was added dropwise to magnesium metal (0.264 g, 11 mmol) and a catalytic amount of iodine at room temperature under a N_2 atmosphere. After the Mg was consumed, corresponding aldehyde (10 mmol) was added in one portion at 0 °C, and the mixture was stirred vigorously for 4–14 h at room temperature. The reaction mixture was neutralized with NH_4Cl solution, and the resulting solution was poured into water and was extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and was evaporated under vacuum. The pure compound was isolated in good yield after purification via flash column chromatography using 15–20% ethyl acetate in hexane as the eluent. *1,2-Diphenylprop-2-en-1-ol* (**1a**): Yield: 81%; yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.18 (br s, 1H, OH), 5.45 (s, 1H, CH), 5.48 (s, 1H, CH), 5.67 (s, 1H, CH), 7.18–7.39 (m, 10H, ArH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 74.24, 114.24, 127.19, 127.25, 127.84, 127.97, 128.46, 128.66, 139.59, 142.08; CG/MS: *m*/*z* (relative, %) 210 (27), 107 (42), 104 (100), 79 (44), 77 (48). *1-(4-Chlorophenyl)-2-phenylprop-2-en-1-ol* (**1b**): Yield: 78%; yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.18 (br s, 1H, OH), 5.46 (s, 1H, CH), 5.50 (s, 1H, CH), 5.68 (s, 1H, CH), 7.22–7.40 (m, 9H, ArH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 75.18, 114.11, 126.80, 127.62, 128.10, 128.14, 128.38, 133.27, 138.74, 140.08, 150.03; CG/MS: *m*/*z* (relative, %) 244 (36), 104 (100), 93 (41), 77 (67).
15. *General procedure for the synthesis of α,β-epoxy ketones* **1a–k**: a solution of the olefinic alcohol (**1a–k**) (0.5 mmol) in dichloromethane (5 mL) in a two-necked round-bottomed flask was cooled to −78 °C under a nitrogen atmosphere. A solution of *m*-chloroperbenzoic acid (172 mg, 1.0 mmol) in dichloromethane (5 mL) was added dropwise. Next, $PdCl_2$ (4.4 mg, 5 mol %) was added, and the reaction solution was stirred for 4–14 h at room temperature. The reaction mixture was diluted with DCM and was washed sequentially with brine and 10% NaOH solution. The organic layer was dried over $MgSO_4$ and then was evaporated under vacuum. The crude product was purified by flash column chromatography using 8–10% ethyl acetate in hexane as the eluent. *Phenyl(2-phenyloxiran-2-yl)methanone* (**2a**)[8]: Yield: 81%; colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.09 (d, *J* = 5.4 Hz, 2H, 2CH), 3.24 (d, *J* = 5.4 Hz, 2H, 2CH), 7.20–7.35 (m, 10H, ArH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 55.07, 125.39, 127.92, 129.29, 128.55, 128.59, 128.84, 130.00, 130.07, 132.42, 133.78, 134.54, 137.63, 196.78; CG/MS: *m*/*z* (relative, %) 224 (17), 208 (12), 121 (63), 105 (100), 91 (39), 77 (33). *(4-Chlorophenyl)(2-phenyloxiran-2-yl)methanone* (**2b**): Yield: 85%; colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.99 (d, *J* = 5.4 Hz, 1H, CH), 3.31 (d, *J* = 5.4 Hz, 1H, CH), 7.18–7.41 (m, 7H, ArH), 7.90 (d, *J* = 9.0 Hz, 2H, ArH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 55.13, 63.10, 125.29, 128.42, 128.62, 129.10, 129.97, 131.38, 132.26, 135.26, 140.34, 193.53; CG/MS: *m*/*z* (relative, %) 258 (13), 242 (6), 165 (15), 141 (32), 139 (100), 119 (62), 105 (26), 91 (60).