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N-Hydroxyphthalimide catalyzed allylic oxidation of steroids with *t*-butyl hydroperoxide

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ABSTRACT

A new and optimized procedure for the allylic oxidation of Δ^5-steroids with *t*-butyl hydroperoxide in the presence of catalytic amounts of N-hydroxyphthalimide (NHPI) under mild conditions was developed, showing excellent regioselectivity and chemoselectivity (functional group compatibility). It was found that $Co(OAc)_2$ could enhance the catalytic ability of NHPI resulting in better yields and shorter reaction times. The reaction mechanism and the scope of the reaction with a variety of Δ^5-steroidal substrates were also investigated.

1. Introduction

Allylic oxidation belongs to an important group of olefin oxidations and remains a reaction of considerable importance in organic chemistry with applications in areas ranging from agricultural products to pharmaceutical [1]. The allylic oxidation of steroids is a particularly important subject and has attracted interest as highly useful synthetic conversions over many years. Among the most frequently encountered oxidation products of Δ^5-steroids are those with a ketone function at C-7. These compounds, which have been found in animal tissues and foodstuffs [2], are known to be inhibitors of sterol biosynthesis [3,4] and with some use in cancer chemotherapy, since they inhibit aromatase activity, [5] cell replication, and are more toxic towards tumor than non-tumor cells [6–8].

Examination of the literature showed that a variety of chromium (VI) compounds have been used in the allylic oxidation [9–20]. However, complications in applying these methods remain because of the harsh reaction conditions required and difficult workup and purification procedures. In addition, the accumulations of chromic acid or chromium salt wastes that are the side products of these reactions are of great environmental concern.

A variety of catalytic methods for allylic oxidation have been reported and generally peroxide-based oxidants have been the reagents of choice. Of greater preparative interest has been the use of *tert*-butyl hydroperoxide (TBHP) combined with different type of metal catalysts. Despite the good yields reported with $RuCl_3$ [21] to prepare allylic oxidation products from Δ^5-steroids, the high cost of the ruthenium catalyst, along with the high risk of the strongly exothermic reaction can result from the accumulation of TBHP in larger scale reactions renders the procedures unsuitable for commercialization and led other researchers to find some new methods for this type of oxidation. To complete such modifications in a more environmentally friendly yet still efficacious manner, many other metal complexes/salts have been employed, such as sodium chlorite, [22] copper catalyst, [23,24] dirhodium caprolactamate, [25] cobalt acetate, [26,27] and manganese (III) acetate [28]. However, numerous limitations remain. All of the available methods must strike a balance between good yields and compatibility with sensitive functionalities near allylic sites (e.g., hydroxyl group). Furthermore, the long reaction time requirements and difficult catalyst preparation are additional disadvantages which often make such processes unattractive.

Recently, a new organic catalyst, N-hydroxyphthalimide (NHPI), has been introduced as an effective catalyst for C—H bond activation by hydrogen abstraction [29], which is a cheap and non-toxic compound easily prepared by the reaction of phthalic anhydride with hydroxylamine [30]. The protagonist, NHPI, catalyzes a wide variety of free radical autoxidations, improving both activities and selectivities by increasing the rate of chain propagation and/or decreasing the rate of chain termination. It is believed that its active catalytic species, phthalimide *N*-oxyl radical (PINO), which is formed *in situ* from NHPI via one electron transfer, initiates the

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radical propagation of autoxidation. The oxidation by molecular oxygen in the presence of NHPI and an organic free-radical initiator such as dibenzoyl peroxide (BPO) or azodiisobutyronitrile have been reported to be suitable for the allylic oxidation of steroids, as it gives moderate yields of Δ^5-7-keto-steroids, and the catalyst can be recovered almost completely thereby avoiding the use of metal compounds and consequently the contamination of product by metal compounds [31–34]. Despite these benefits, the stoichiometric amounts of NHPI must be used and the application of this method to the laboratory scale is restricted due to the technical and safety problems related to a reaction under an oxygen atmosphere. Herein, we report the use of inexpensive and commercially available cobalt acetate and NHPI (catalytic amounts) as the catalyst and of *tert*-butyl hydroperoxide (TBHP) as the cooxidant for mild, efficient, regioselective, chemoselective (functional group compatible), allylic oxidation of different Δ^5-steroids. As far as we are aware, it is the first demonstration of allylic oxidation by *tert*-butyl hydroperoxide (TBHP) in cooperation with NHPI. This allylic oxidation process, requiring fewer reagents, shorter reaction time, no specialty chemicals, no expensive anhydrous solvents and employing mild reaction conditions and easy work-up, has provided a milder and inexpensive approach for the synthesis of this important class of compounds.

2. Experimental

Melting points were determined using WRR melting point apparatus. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AV-400 spectrometer (Bruker Corporation, America) at working frequencies 400 and 100 MHz respectively in $CDCl_3$ and with TMS as the internal standard. Chemical shifts are expressed in ppm downfield from TMS and observed coupling constants (J) are given in Hertz (Hz). Starting materials were commercially purchased. The progress of the reactions was monitored by thin-layer chromatography (TLC) Analytical thin-layer chromatography (TLC) was conducted using silica gel plates (200 microns) containing a fluorescent indicator (silica gel 60 F_{254}). Detection was performed by spraying with phosphomolybdic acid (5%) and heating at 120 °C. Column chromatography was performed using silica gel, 200–300 mesh, and elution was performed with *n*-hexane/ethyl acetate.

2.1. General procedure for allylic oxidation of the Δ^5-steroidal substrates

In a typical experiment, to a solution of 25-hydroxycholesteryl acetate (0.428 g, 1 mmol) in acetone (10 mL), NHPI (0.0163 g, 0.1 mmol), $Co(OAc)_2$ (0.002 g, 0.01 mmol) and TBHP (0.515 g, 4 mmol) were added. After 12 h under magnetic stirring at ambient temperature (TLC monitoring), the solution was poured into sodium sulfite solution (10% aq.) and extracted with dichloromethane. The extract was washed with an aq. saturated solution of $NaHCO_3$, water, dried over anhydrous sodium sulfate, and evaporated. The final products were isolated using column chromatography (absorbent: silica gel, mobile phase: *n*-hexane/EtOAc (8:1, v/v)).

11 [19]: Isolated as a white solid; mp: 148.2–149.7 °C (lit. mp: 150 °C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.63 (d, J = 1.5 Hz, 1H), 4.64 (m, 1H), 0.87 (d, J = 6.5 Hz, 3H), 0.61 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 200.93, 169.28, 162.86, 125.68, 71.19, 70.07, 53.69, 48.92, 48.76, 44.38, 43.36, 42.10, 37.63, 37.29, 36.72, 35.41, 34.97, 34.67, 28.23, 26.33, 25.27, 20.25, 20.14, 19.78, 17.81, 16.24, 10.95.

12 [19]: Isolated as a white solid; mp: 178.4–180.5 °C (lit. mp: 183.5–184 °C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.62 (d, J = 1.4 Hz, 1H), 3.60 (m, 1H), 0.87 (d, J = 6.5 Hz, 3H), 0.61 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 201.26, 164.25, 125.07, 70.10, 69.47, 53.79, 49.00, 48.96, 44.41, 43.40, 42.14, 40.84, 37.73, 37.29, 35.47, 35.38, 34.67, 30.19, 28.31, 28.23, 27.55, 25.30, 20.23, 19.81, 17.85, 16.31, 10.98.

13 [29]: Isolated as a white solid; mp: 158.3–159.8 °C (lit. mp: 154–155 °C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.63 (d, J = 1.6 Hz, 1H), 4.65 (m, 1H), 1.98 (s, v3H), 1.14 (s, 3H), 0.85 (d, J = 6.5 Hz, 3H), 0.80 (d, J = 6.6 Hz, 3H), 0.79 (d, J = 6.6 Hz, 3H), 0.61 (s, 3H).^{13}C NMR ($CDCl_3$, 100 MHz): δ 200.98, 169.29, 162.85, 125.69, 71.20, 53.74, 48.93, 48.78, 44.40, 42.09, 38.45, 37.63, 37.29, 36.72, 35.15, 34.97, 34.70, 27.52, 26.97, 26.33, 25.29, 22.80, 21.79, 21.54, 20.25, 20.14, 17.84, 16.24, 10.9.

14 [35]: Isolated as a white solid; mp: 168.5–170.5 °C (lit. mp: 169–171 °C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.62 (d, J = 1.6 Hz, 1H), 3.60 (m, 1H), 1.13 (s, 3H), 0.85 (d, J = 6.5 Hz, 3H), 0.80 (d, J = 6.5 Hz, 3H), 0.79 (d, J = 6.5 Hz, 3H), 0.61 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 201.39, 164.24, 125.06, 69.47, 53.78, 48.95, 48.92, 44.40, 42.09, 40.80, 38.46, 37.69, 37.27, 35.33, 35.17, 34.69, 30.15, 27.52, 26.98, 25.30, 22.81, 21.79, 21.54, 20.20, 17.85, 16.29, 10.95.

15 [23]: Isolated as a white solid; mp: 148.8–150.1 °C (lit. mp: 150–153 °C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.65 (d, J = 1.6 Hz, 1H), 4.66 (m, 1H), 2.06 (s, 3H), 1.99 (s, 3H), 1.15 (s, 3H), 0.59 (s, 3H).^{13}C NMR ($CDCl_3$, 100 MHz): δ 208.67, 200.14, 169.28, 163.17, 125.50, 71.08, 61.26, 48.98, 48.65, 44.23, 43.37, 37.37, 36.76, 36.63, 35.01, 30.60, 26.30, 25.44, 22.60, 20.23, 20.08, 16.25, 12.24.

16 [26]: Isolated as a white solid; mp: 205.9–207.0 °C (lit. mp: 207–208 °C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.64 (d, J = 1.7 Hz, 1H), 3.61 (m, 1H), 2.06 (s, 3H), 1.14 (s, 3H), 0.59 (s, 3H).^{13}C NMR ($CDCl_3$, 100 MHz): δ 208.81, 200.57, 164.64, 124.84, 69.37, 61.29, 49.00, 48.77, 44.22, 43.40, 40.84, 37.34, 36.67, 35.37, 30.59, 30.10, 25.46, 22.60, 20.13, 16.31, 12.24.

17 [26]: Isolated as a white solid; mp: 182.9–184.5 °C (lit. mp: 184–185 °C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.69 (d, J = 1.4 Hz, 1H), 4.65 (m, 1H), 2.76 (m, 1H), 1.99 (s, 3H), 1.17 (s, 3H), 0.83 (s, 3H).^{13}C NMR ($CDCl_3$, 100 MHz): δ 219.23, 199.72, 169.26, 163.82, 125.51, 70.95, 48.95, 46.84, 44.72, 43.34, 37.44, 36.82, 34.95, 34.62, 29.67, 26.27, 23.15, 20.22, 19.53, 16.37, 12.74.

18 [26]: Isolated as a white solid; mp: 221.4–223.6 °C (lit. mp: 229–232 °C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.68 (d, J = 1.4 Hz, 1H), 3.63 (m, 1H), 2.75 (m, 1H), 1.16 (s, 3H), 0.83 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 219.42, 200.08, 165.19, 124.89, 69.28, 49.08, 46.86, 44.73, 43.32, 40.85, 37.40, 35.29, 34.63, 30.09, 29.70, 23.16, 19.57, 16.42, 12.74.

19 [29]: Isolated as a white solid; mp: 184.5–185.5 °C (lit. mp: 183.8–184 °C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.71 (d, J = 1.3 Hz, 1H), 4.72 (m, 1H), 4.48 (m, 1H), 3.44 (m, 2H), 2.87 (m, 1H), 2.49 (m, 3H), 2.05 (s, 3H), 1.23 (s, 3H), 0.98 (d, J = 7.0 Hz, 3H), 0.80 (s, 3H) 0.79 (s, 3H).^{13}C NMR ($CDCl_3$, 100 MHz): δ 201.36, 170.28, 164.08, 126.50, 109.19, 80.93, 72.14, 66.80, 61.09, 49.65, 49.46, 44.89, 41.58, 40.97, 38.66, 38.46, 37.79, 35.99, 33.71, 31.44, 30.31, 28.80, 27.33, 21.24, 20.90, 17.26, 17.12, 16.43, 14.65.

20 [36]: Isolated as a white solid; mp: 192.4–194.5 °C (lit. mp: 198–203 °C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.63 (d, J = 1.6 Hz, 1H), 4.39 (m, 1H), 3.36 (m, 2H), 2.80 (m, 1H), 2.39 (m, 3H), 1.15 (s, 3H), 0.91 (d, J = 7.0 Hz, 3H), 0.73 (s, 3H) 0.72 (s, 3H).^{13}C NMR ($CDCl_3$, 100 MHz): δ 200.71, 164.40, 124.87, 108.20, 79.93, 69.42, 65.79, 60.07, 48.78, 48.47, 43.85, 40.85, 40.56, 39.94, 37.70, 37.40, 35.32, 32.69, 30.41, 30.13, 29.30, 27.77, 19.93, 16.31, 16.11, 15.42, 13.63.

3. Results and discussion

In a first set of experiments, 25-hydroxycholesterol acetate was used as a model substrate under various experimental conditions (Table 1). Acetone was chosen as solvent to dissolve steroids.

A generally increasing trend of isolated yield was observed as the amount of NHPI was increased from 0.1 equiv to 2 equiv. The highest yield was achieved when 1.0 equiv of NHPI was used, and the additional amount of NHPI did not result in a higher yield (Table 1, entries 1–4). To ensure that the reaction gives the desired yield, stoichiometric amount of NHPI must be used. Lesser amounts of catalysts and higher yields of products were always the ultimate goal in industrial application. Thus it is crucial for the oxidation of 25-hydroxycholesterol acetate using a catalytic amount NHPI in high yield. However, as shown in Table 1, when the amount of NHPI was dropped to 0.5 equiv, both the reaction rate and yield significantly decreased.

Early research indicated that NHPI can efficiently oxidate substrate by adding a small amount of radical starters, such as dibenzoyl peroxide (BPO). However, stoichiometric amount of NHPI was still needed (Table 1, entries 5 and 6). In combination with transition metal salts co-catalysts, notably cobalt, the reactivity of NHPI can be enhanced. [37] Thus, transition metal salts was added to the reaction as co-catalyst. The improved yields and shorter reaction times were obtained only with catalytic amounts of NHPI (Table 1, entries 7–11). Interestingly, we noticed that the yields were improved to some extent no matter what kind of metal salt was used. Among the screened co-catalyst, the yields were lower when trivalent metal salts were used, while the higher yields were obtained when bivalent metal salts were used. NHPI acts as a precursor of the phthalimido-*N*-oxyl (PINO) radical, generated with the assistance of metal salts. The transition metal ions worked by forming oxo-transition metal intermediates. This required the transition metal ions have the ability to lose one electron (e.g., Co(II)–Co(III)), which may explain why bivalent metal salts are more effective than trivalent ones that are far more reluctant to lose electrons. [38] Blank experiments revealed that $Co(OAc)_2$ as the sole catalyst led to a longer reaction time. No significant reaction occurred in the absence of catalyst (Table 1, entries 12 and 13). To find the best catalytic system, allylic oxidation of 25-hydroxycholesterol acetate in the presence of other nitroxy radicals under the same conditions was studied. 2,2,6,6-Tetramethylpiperidinel-oxyl (TEMPO), being a widely used catalyst for the oxidation of alcohols, was used in our allylic oxidation system, had no catalytic activity under these conditions (Table 1, entry 14). The use of N-hydroxysuccinimide (NHSI) in place of NHPI led an increase in the reaction time and lower yield (Table 1, entry 15). Based on the above-mentioned results, NHPI was revealed to be a key catalyst proved efficient both with respect to the final yields and the reaction times.

Table 1
Allylic oxidation of 25-hydroxycholesterol acetate.[a]

Entry	Catalyst/mmol	Co-catalyst/mmol	Time/h	Yield[b]/%
1	NHPI (0.1)	–	36	10.0
2	NHPI (0.5)	–	36	45.8
3	NHPI (1)	–	24	61.9
4	NHPI (2)	–	18	58.8
5[c]	NHPI (1)	BPO (0.05)	12	69.5
6[c]	NHPI (0.5)	BPO (0.05)	18	55.8
7	NHPI (0.1)	$Co(OAc)_2$ (0.01)	12	74.3
8	NHPI (0.1)	$Mn(OAc)_2$ (0.01)	18	68.3
9	NHPI (0.1)	$Cu(OAc)_2$ (0.01)	30	55.9
10	NHPI (0.1)	$Co(acac)_3$ (0.01)	18	44.4
11	NHPI (0.1)	$Fe(acac)_3$ (0.01)	10	30.5
12	–	$Co(OAc)_2$ (0.01)	48	60.5
13	–	–	48	–
14	TEMPO (0.1)	$Co(OAc)_2$ (0.01)	48	–
15	NHSI(0.1)	$Co(OAc)_2$ (0.01)	18	51.3

[a] Reaction conditions: 25-hydroxycholesterol acetate (1 mmol), acetone (10 mL), TBHP (4 mmol), room temperature.
[b] Isolated yield.
[c] The reaction was heated to 50 °C.

Solvent was an important variable for this oxidation. Among the screened solvents, acetone was found to be the best solvent (Table 2, entry 2). No significant changes were seen when the reaction temperatures changed from 50 °C to 25 °C (Table 2, entries 1 and 2). A generally increasing trend of isolated yields was observed as the oxidant ratio was increased from 1 equiv to 6 equiv. The highest yield was achieved when 4 equiv of TBHP was used, and the additional amount of oxidant did not result in a higher yield. Compared to other reported TBHP-mediated oxidation, [21,23,24,26,27] fewer reagents were used.

The scope of the present procedure was further indicated by the results summarized in Table 3 for a variety of Δ^5-steroidal substrates (Scheme 1).

In most cases examined, the reactions proceeded smoothly using the optimized condition with 10 mol% of NHPI, 4 equiv of TBHP, 1 mol% of $Co(OAc)_2$ and acetone as the solvent at ambient temperature. The allylic oxidation products were obtained in isolated yields, in the range 59.9–93.7%. The excellent chemoselectivity of the reaction was noteworthy. High selectivity was found towards the formation of steroidal enones even when a free secondary hydroxyl group was present. The more challenging oxidation of 3-hydroxy-Δ^5-steroids can be successfully realized with a small decrease in yields. Interestingly, we found that even when the same method was applied for different substrates, a fluctuant degree of yields and reaction time were achieved.

For Δ^5-steroids, the two allylic sites do not have much difference in reactivity at first glance. However, only 7-keto products were obtained exclusively. From the resonance structures, the difference became clear (Fig. 1). Species bearing a radical at the 7-position will have two possible resonance structures, one of which is a tertiary radical that can significantly lower the energy,

Table 2
Oxidation of 25-hydroxycholesterol acetate by TBHP/NHPI/$Co(OAc)_2$ in different conditions.[a]

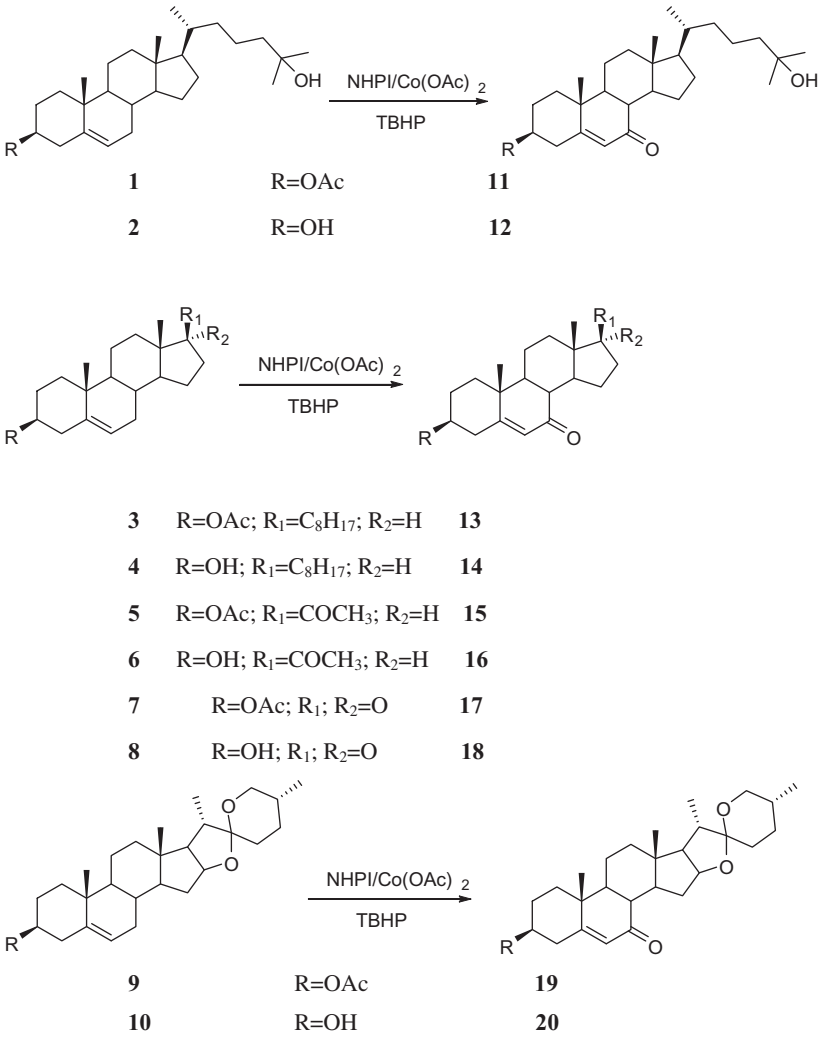
Entry	TBHP/mmol	Solvent	*T*/°C	Time/h	Yield[b]/%
1	4	Acetone	50	11	69.1
2	4	Acetone	25	12	74.3
3	1	Acetone	25	24	24.6
4	2	Acetone	25	15	50.0
5	6	Acetone	25	12	73.0
6	4	THF	25	48	–
7	4	1,2-Dioxane	25	48	–
8	4	EtOAc	25	24	35.1
9	4	CH_2Cl_2	25	24	15.0

[a] Reaction conditions: 25-hydroxycholesterol acetate (1 mmol), solvent (10 mL), NHPI (0.1 mmol), $Co(OAc)_2$ (0.01 mmol).
[b] Isolated yield.

Table 3
Allylic oxidation of Δ^5-steroidal substrates.[a]

Entry	Substrate	Product	Time/h	Yield[b]/%
1	1	11	12	74.3
2	2	12	12	59.9
3	3	13	12	75.8
4	4	14	12	63.8
5	5	15	7	85.9
6	6	16	7	73.5
7	7	17	5	93.7
8	8	18	5	81.1
9	9	19	11	75.5
10	10	20	11	63.0

[a] Reaction conditions: Δ^5-steroidal substrates (1 mmol), acetone (10 mL), TBHP (4 mmol), $Co(OAc)_2$ (0.01 mmol), NHPI (0.1 mmol), room temperature.
[b] Isolated yield.



Scheme 1. Chemical structures of the starting Δ^5-steroidal substrates and the final Δ^5-7-keto derivatives.

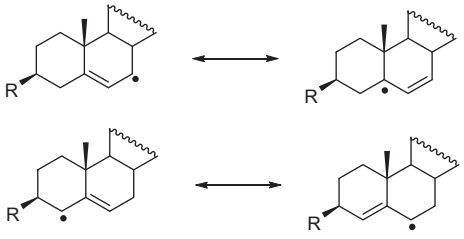


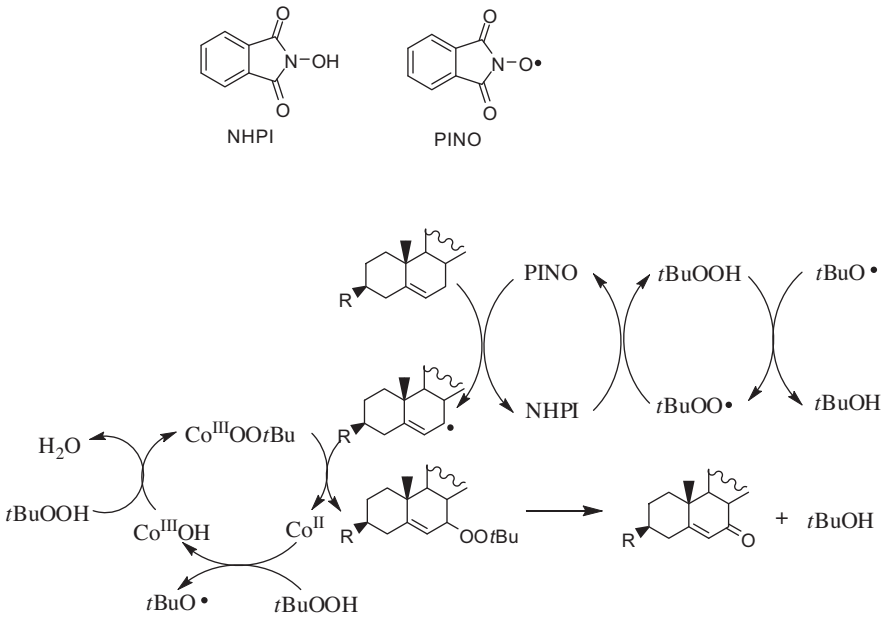
Fig. 1. Resonance structures of radical species at the 7-position or at the 4-position.

while the species bearing a radical at the 4-position also has two possible resonance structures, but neither contributes to the lower energy state. Meanwhile, it is to be expected that axial hydrogen will be preferentially abstracted to equatorial hydrogen because of the more favorable stereoelectronic situation with the developing p-orbital and the π system. [39] In this case, the axial hydrogen of C-4 lies above the plane of the steroid molecule, and the angular methyl group at C-10 would hinder the approach of the oxidizing species. The axial hydrogen at C-7, which is below the plane of the molecule, is free from such steric interferences. Thus the reaction proceeded at this position to yield the corresponding Δ^5-7-keto products.

The mechanism of the allylic oxidation is worth considering. Allylic oxidation is a process involving free radicals, and it is most likely to occur in the presence of low oxidation state transition metal species. A plausible reaction mechanism for the allylic oxidation catalyzed by NHPI and transition metal salts is shown in Scheme 2.

The *in situ* generation of PINO from NHPI through redox reaction of transition metal salts is a key step. Once PINO is generated the autoxidation can proceed further by the chain propagation steps, which involves selective allylic hydrogen abstraction to generate the allyl radical, transfer of the *tert*-butyl peroxy ligand from the metal center to the allyl radical, and the *t*-butoxy radical promoted degradation of the *tert*-butyl peroxy ether to the corresponding enone.

In summary, a mild, efficient, regioselective, and highly functional group compatible allylic oxidation protocol using commercially available NHPI and $Co(OAc)_2$ as the catalyst has been developed. Compared to other TBHP-mediated methods, this system was proved to be efficient both with respect to the final yields and the compatibility with sensitive functionalities near allylic sites (e.g., hydroxyl group). This economical and environmentally-friendly procedure led to good yields with a small amount of catalyst in a relative short reaction time and can be conveniently scaled-up for subsequent manufacturing and commercialization.



Scheme 2. A plausible mechanism for the allylic oxidation of Δ^5-steroidal substrates catalyzed by NHPI and $Co(OAc)_2$.

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