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Organopromoted Selectivity-Switchable Synthesis of Polyketones

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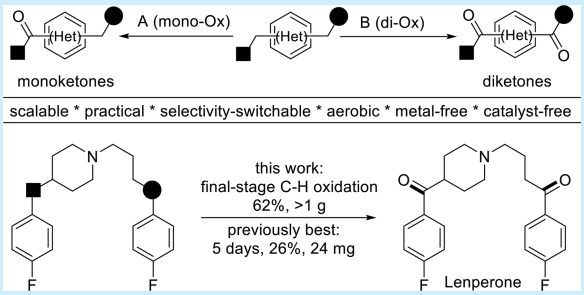
Supporting Information

ABSTRACT: In this work, an organopromoted metal-free pharmaceutical-oriented selectivity-switchable benzylic oxidation was developed, affording mono-, di-, and trioxygenation products, respectively, using oxygen as the oxidant under mild conditions. This process facilitates dioxygenation of 2,6-benzylic positions of heterocycles, which could be inhibited by heterocycle chelation to the metal cocatalysts. Enantiopure chiral ketones could also be prepared. The noninvolvement of transition metals and toxins avoids metal or hazardous residues, consequently ensuring a final-stage gram-scale synthesis of Lenperone.



In recent decades, methods for synthesis of aromatic ketones[1−10] have been well established, since aromatic ketones are useful feedstocks in organic synthesis, representing convenient intermediates for manufacturing pharmaceuticals (Figure 1). Conventional methods, such as the Friedel−Crafts

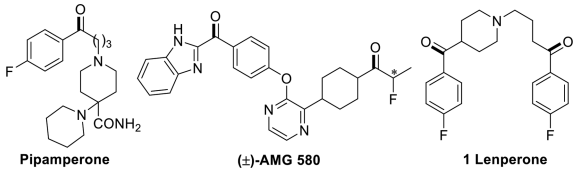
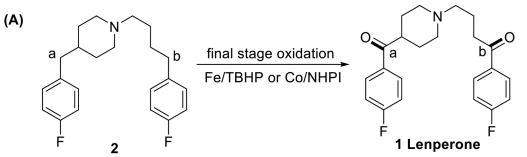


Figure 1. Representative pharmaceuticals containing polyketones.

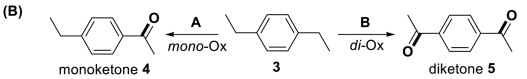
reaction, could afford monoketones successfully via an electrophilic aromatic substitution. However, the ketone products are less reactive than their precursors due to the electron-withdrawing effect of their carbonyl group, giving rise to the nonoccurrence of multiple acylations which are necessary for the generation of polycarbonyl arenes. Despite being seemingly simple, the synthesis of di- or polyketone remains a challenge.[5b,7b,h,i,8d−f,9c]

Considering alkylarenes are inexpensive and abundant industrial materials, the synthesis of aromatic ketones by oxygenation of a benzylic C−H bond under environment-friendly conditions has attracted much attention.[2−8] However, it is difficult to obtain dioxygenation products as a result of the electron-withdrawing effect of the carbonyl groups on the ketone intermediates which are less reactive than their original molecules. For example, the oxygenation with IBX could only convert diethylbenzene to monoketone **4**, but failed to give dioxygenation product **5** (Table 1).[2] Similarly, Co- or Cu-catalyzed aerobic benzylic oxygenation,[3,4] which has been successfully applied in the synthesis of monoketones, could not afford the dioxygenation product **5** either (Table 1). Despite

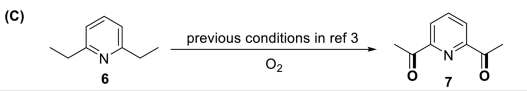
Table 1. Dioxygenation of 2, 3, and 6 with Reported Methods



entry	ref	conditions	**1** (%)
1	3h	Fe/acid/pyridine, TBHP, MeCN, rt, N_2, 5 days	26 (24 mg)
2	3a, 3d	NHPI, PhCN, 100 °C or TBAB, $PhCF_3/H_2O$, 80 °C	0
3	3f	Co/Mn/NHPI (cat.), AcOH, 130 °C	0
4	3b-c, g	Co/NHPI (cat.), MeCN or AcOH or HFIP, rt-100 °C	0
5	3g	Co/NHPI, MeCN, 75 °C (only 20% of monoketone at site-b was observed)	0



ref	conditions	**4** (%)	ref	conditions	**5** (%)
2	IBX, DMSO/PhF, 85 °C	57%	2	IBX, DMSO/PhF, 85 °C	0%
3	$Co(OAc)_2$, NHPI, O_2, 90 °C	61	3	$Co(OAc)_2$, NHPI, O_2, 90 °C	0
4c	$CuCl_2$, DMF, O_2, 130 °C	0%	4c	$CuCl_2$, DMF, O_2, 130 °C	0%



entry	ref	conditions	**7** (%)
1	3	Co/NHPI, BuOAc, 90-100 °C	0
2	3b, c, g, i	Co/NHPI, MeCN or AcOH or HFIP, rt-100 °C	0
3	3f	Co/Mn/NHPI, AcOH, 130 °C	0
4	3a, d	NHPI, PhCN, 100 °C, or TBAB, $PhCF_3/H_2O$, 80 °C	0

there being few examples of selective dioxygenation, a ratio of only around 2:1 has been achieved.[7b,l,8d] In addition, the control of mono-/di-/polyselectivity is even more challenging when

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there are more than two benzyl sites in the substrates. Moreover, in the aforementioned approaches, toxic organics as well as high-valent transition metals have been widely used as oxidants, causing the problem of the removal of residual metal/toxics in the products which limits their applications in pharmaceutical synthesis. Therefore, the development of a transition-metal-free and selectivity-switchable oxygenation is essential for a pharmaceutically oriented synthesis.

Lenperone **1** (Figure 1) is a typical antipsychotic of the butyrophenone chemical class. Using a strategy of final stage oxygenation, the previously reported Fe−$PyCO_2H$−^{t}BuOOH system afforded only 24 mg of Lenperone **1** in 26% isolated yield after 5 days of oxidation (Table 1A, entry 1).[3h] We also screened the reported catalytic Co/NHPI system (entries 2−5), but no dioxygenation reaction occurs. Thus, the dioxygenation of compound **2** to Lenperone via a final stage oxidation remains as an unsolved issue in organic synthesis.

Encouraged by the unsuccessful trial in the above-mentioned issue, the synthesis of ketones via the selectivity-switchable benzylic oxygenation was then explored with common methods[2−4] in the oxidation of **3** to monoketone **4** or diketone **5** as a model reaction and the results are summarized in Table 1B. Methods using IBX or cobalt catalysts afforded mono-oxygenation product **4** as the only product in moderate yields, but the copper system totally failed (left column). Unfortunately, dioxygenation product **5** did not occur in any previous conditions (right column).

Pyridine-containing alkyl heteroarenes are difficult to react utilizing the benzylic C−H oxidation and special protecting strategy that has been employed in previous work.[4c] We then tested dioxygenation of pyridine-containing substrate **6** in which the ethyl substituent is directly adjacent to a coordinating *N*-atom (Table 1C). In transition-metal catalysis, the pyridine core can inhibit the oxygenation by chelation to the metal cocatalyst.[3j] Neither Ishii's or Stahl's procedure can be used as an alternative for such substrates (entries 1−4).

Thus, all aforementioned reported methods *failed* to realize either the *dioxygenation* of dialkyl arene **5** or *pyridine-containing heteroarene* **7**. Therefore, a new method must be established for dioxygenation of such dialkyl arenes and heteroarenes. Recently, we reported that an *N*-hydroxyphthalimide (NHPI)/^{t}BuONO (TBN) system could generate benzyl radicals and provide an efficient approach to mono-/diselectivity control in aromatic nitrile synthesis.[11a] Herein we report our latest results in the development of a NHPI/^{t}BuONO[12] promoted selectivity-switchable benzylic oxidation in the presence of O_2 to achieve mono-, di-, and polyoxygenation products, using a strategy of an organopromoted interrupted radical trapping process (Figure 2).

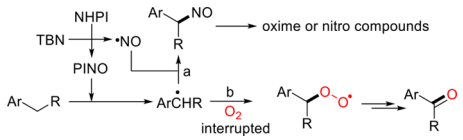
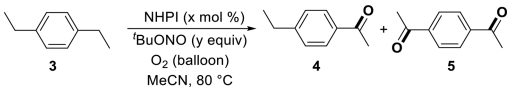


Figure 2. Working model of oxygen interruption.

The rapid interruption of oxygen over NO in trapping benzylic radical intermediates enables the oxygenation over amination. This transition-metal-free and toxic-free synthetic method provides a practical and convenient access to pharmaceuticals containing substituted aromatic ketones from environmental and economic viewpoints.

To investigate the conditions for controlling the selectivity between mono- and dioxygenation, diethylbenzene **3** was subjected to various reaction conditions in the presence of NHPI and TBN under O_2. Only monoketone **4** was obtained with 0.5 equiv of NHPI and 1 equiv of TBN (Table 2, entry 3),

Table 2. Selectivity Control



entry	*x*	*y*	atmosphere	**4** (%)[b]	**5** (%)[b]
1	30	3	O_2	57	0
2	50	3	O_2	62	12
3	50	1	O_2	84	trace
4	50	0.5	O_2	60	5
5	100	2	O_2	0	73
6	50	1	argon	23	0
7	50	1	air	42	0

[a]Conditions: **1a** (0.5 mmol), O_2 (1 atm)^{t}BuONO, NHPI, dry MeCN (1 mL), 80 °C, 24 h. [b]By ^{1}H NMR with internal standards.

whereas the product was switched to dioxygenation product **5** when 1 equiv of NHPI and 2 equiv of TBN were employed (entry 5). Thus, the selectivity of mono-/dioxygenation was synergistically controlled by the amount and ratio of TBN/NHPI. The reaction under argon or air lowered the yield of **4** (entries 6 and 7), indicating that O_2 is a necessary oxidant in this reaction. The reaction conditions demonstrated in entries 3 and 5 were then chosen as the standard conditions for mono- and dioxygenation, respectively. These results again demonstrate the advantage of our approach over metal catalysis in the oxidation of heterocycles bearing a chelating groups. Despite the fact that substoichiometric or stoichiometric NHPI has to be employed, our metal-free method shows advantages in selective dioxygenation of alkylarenes and potential utility in substituted ketone synthesis. Although the regeneration of PINO with TBN/O_2 or O_2 alone is possible in principle, the efficiency is not high. Stoichiometric TBN enables the sufficient generation of a high concentration of the PINO radical which is needed for the generation of radicals from less reactive electron-deficient substrates or intermediates.

Subsequently, the scope of the substrate has been investigated under optimized conditions to evaluate the control of selectivity between mono- and dioxygenation (Table 3). A wide range of mono- and dioxygenation products have been selectively prepared from corresponding dialkylarenes. For example, under standard Condition A, a variety of monoketones have been obtained in generally good yields (left column). Pyridine-containing substrates were selectively converted to monoketone **8** and diketone **7** in 63% and 54% yields, respectively. Either *para*- or *meso*-diethylbenzene afforded corresponding monoketone **4** or **9** in an 82% or 80% isolated yield. The gram-scale synthesis shows synthetic capability in preparation (**9** and **10**). In all cases, the selectivity was good and only trace dioxygenation products were observed. The regioselectivity is consistent with the stability of the radical pathway, in which the diaryl benzyl position is prior to the ethyl side (**11**). On the other hand, under standard Condition B, various dioxygenation products were achieved, in which no monoketones were observed (right column).

Enantioenriched alkylarenes could be oxidized to afford mono- and dioxygenation products while retaining ee-values (Scheme

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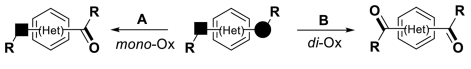
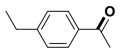
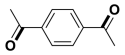
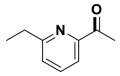
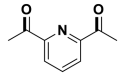
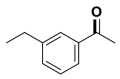
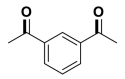
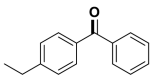
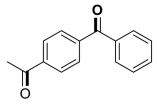
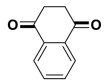
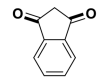
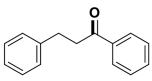
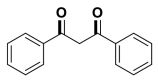
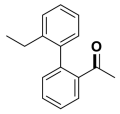
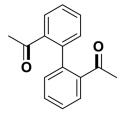
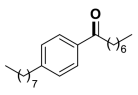
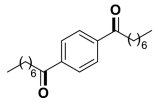
Table 3. Selectivity-Switchable Synthesis of Polyketones[a]

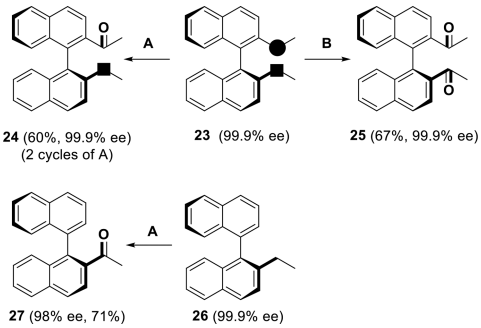


monoketone	yield (%)	diketone	yield (%)
	**4** (82%)		**5** (71%)
	**8** (63%)		**7** (54%)
	**9** (80%) (74%, 1.23 g)		**10** (73%) (70%, 1.3 g)
	**11** (73%)		**12** (81%)
	**13** (72%)		**14** (86%)
	**15** (78%)		**16** (61%)
	**17** (74%)		**18** (62%)
	**19** (78%)		**20** (73%)
	**21** (70%)		**22** (61%)

[a]Condition A: dialkyl arene (0.5 mmol), O_2 (1 atm), NHPI (0.25 mmol), ^{t}BuONO (0.5 mmol), CH_3CN (1.0 mL), 80 °C, isolated yield. Condition B: same as standard Condition A, except that 0.5 mmol of NHPI and 1.0 mmol of ^{t}BuONO were used.

1). For example, mono-oxygenation product **24** and dioxygenation product **25** were both achieved in 99.9% ee from their

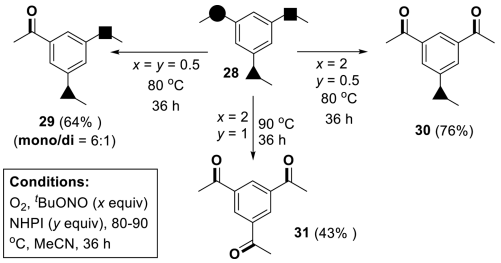
Scheme 1. Synthesis of Enantiopure Ketones



enantiopure precursor **23**. Chiral monoketone **27** was obtained in 98% ee using standard Condition A.

To further examine the capability of controlling selectivity, this method was tested in the oxygenation of 1,3,5-triethylbenzene **28** by simply tuning the ratios of ^{t}BuONO/NHPI (Scheme 2). All three oxygenation products **29**, **30**, and **31** could be selectively obtained with moderate to good yields in 36 h. The synthesis of triketone **31** was performed at 90 °C to obtain full

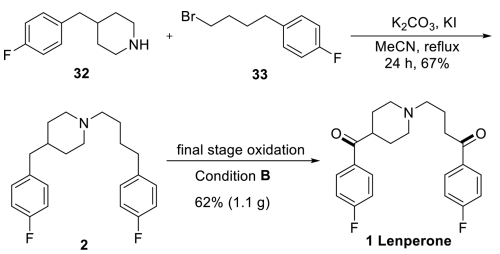
Scheme 2. Mono-, Di-, and Polyoxygenation



conversion of **28**. In each case, high selectivity was achieved, indicating the ability of precise control of the selectivity.

Finally, in the pharmaceutically oriented synthesis, Condition B could afford 1.1 g of Lenperone **1** in 62% of yield (Scheme 3)

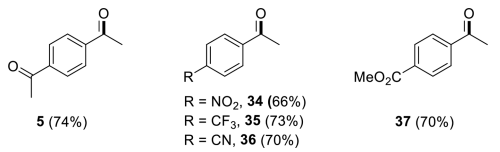
Scheme 3. Gram-Scale Final-Stage C−H Oxidation to Lenperone



without the involvement of any metal (see above-mentioned Table 1), indicating the potential application of the current method in pharmaceutical manufacturing. The standard condition affords only Lenperone **1** with neither monoketones nor the byproducts from the oxidation of *N*-atom or *N*-α-positions.

More examples of electron-deficient substrates are shown in Scheme 4. The electron-withdrawing groups such as NO_2-, CF_3-, Ac, nitrile, and ester are all feasible.

Scheme 4. Electron-Deficient Ketones under Condition B



TEMPO efficiently inhibits the oxygenation of ethylbenzene to acetophenone (eq 1), suggesting that this oxygenation proceeds via a radical process. Phthalimide-*N*-oxyl (PINO) generated from NHPI could abstract the benzylic hydrogen atom of ethylbenzene to form alkyl radicals.[3]

A reaction mechanism is proposed in Scheme 5. The PINO radical is generated by the reaction of NHPI and TBN. PINO abstracts a hydrogen to form the benzyl radical **A**, which is rapidly trapped by oxygen to form intermediate **B**. Monoketone **C** is formed from rearrangement of **B**.[3] The stoichiometric TBN generates sufficient concentration of PINO, enabling further formation of radical intermediates of electron-deficient acetyl **C**. Thus diketone **D** is afforded after the second oxygenation.

In conclusion, we have developed a pharmaceutically oriented synthetically practical and scalable method for the selectivity-switchable approach to mono-, di-, and polyoxygenation via a highly efficient aerobic benzylic oxidation of alkylarenes. This

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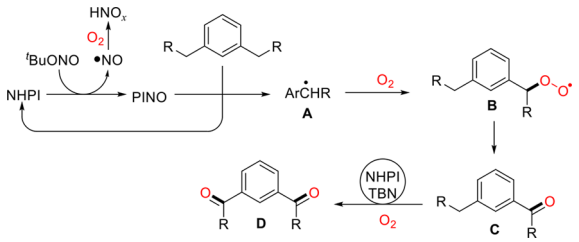
Scheme 5. Proposed Mechanism



metal-free process facilitates dioxygenation of 2,6-benzylic positions of heterocycles, which could be inhibited by heterocycle chelation to the metal cocatalyst in Co-catalysis. The noninvolvement of transition metals and toxins avoids metal or toxic residues, ensuring its applications in pharmaceutical synthesis, demonstrating the advantage of this metal-free condition.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02731.

Experimental details and spectroscopic data for all products (PDF)

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Notes

The authors declare no competing financial interest.

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