

Direct Benzylic Oxidation with Sodium Hypochlorite Using a New Efficient Catalytic System: TEMPO/Co(OAc)₂

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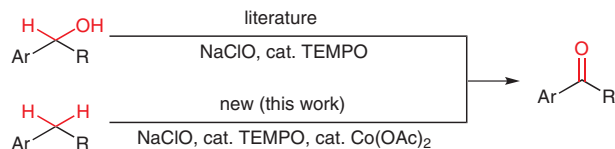
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Abstract: Direct benzylic oxidation of arenes was achieved using NaClO/TEMPO/Co(OAc)₂. Various aromatic aldehydes and ketones were obtained from alkylarenes directly by benzylic oxidation in good to excellent yields. The reaction reactivity, selectivity, and scope of the reaction were investigated.

Key words: benzylic oxidation, arenes, transition metals, TEMPO, sodium hypochlorite

The direct benzylic C–H oxidation of alkylaromatics has greater industrial importance due to its broad application in the manufacture of agrochemicals and pharmaceuticals.¹ Numerous methods have been devised for introducing a carbonyl group at the benzylic position. Conventionally, aromatic ketones are produced through stoichiometric metal oxidants such as chromium(VI)² and KMnO₄.³ In the last few years, other methods have been reported, for example, NaBiO₃/AcOH,⁴ NHPI/O₂,⁵ Mn(III)–salen complex/iodosobenzene,⁶ [PhIO]_n/KBr/H₂O.⁷ Although significant improvements have been made in this area, there still exists several limitations: the corrosive nature of the solvent, tedious working procedures, and narrow scope of the oxidation reaction. Recently, the use of *t*-BuOOH combined with noble-metal catalysts was of particular interest. This includes Rh₂(cap)₄,⁸ KAuCl₄·0.5H₂O,⁹ Ru(III) complex,¹⁰ etc. But the high cost of the Rh, Ru, and Au catalysts motivated the search for cheaper methods based on copper and cobalt catalysts. Thus, the drive towards widely usable and comparatively economical synthetic technologies is challenging and likely to be a subject of long-term interest.




Scheme 1

The well-known nitroxyl radical TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl radical) is a water-soluble and stable oxidation catalyst¹¹ and has been extensively used

in the catalytic oxidation of alcohols to the corresponding aldehydes and ketones under aqueous conditions.¹² In this paper, we report that TEMPO is special in catalytic benzylic oxidation with high selectivity (Scheme 1). To the best of our knowledge, this study represents the first example of using TEMPO for this benzylic oxidation process.

Using diphenylmethane (**1a**) as a model substrate, the oxidation reaction with NaClO was investigated under various experimental conditions (Table 1). Blank experiments revealed that using NaClO alone led to trace of product (entry 1). In the presence of a catalytic amount of TEMPO, benzophenone (**2a**) was obtained in only 38% yield at 0–5 °C (Table 1, entry 2). It was found that certain metal additives could significantly facilitate this benzylic oxidation. For example, Co(OAc)₂ showed especially high efficiency (Table 1, entry 3). Ni(OAc)₂ showed similar reactivity as compared to Co(OAc)₂ (Table 1, entry 7). The Co-facilitated reaction proceeded even at room temperature, albeit with diminished efficiency (Table 1, entry 10). However, Cu salts, known to be effective cocatalysts for the oxidation of alcohols using TEMPO,^{12b} displayed slight improvement (Table 1, entries 8 and 9). Decreasing the amount of TEMPO or NaClO led to lower yields (Table 1, entries 4–6). Among all screened solvents, the best results were obtained in CH₂Cl₂. When the reaction was conducted at the pH value of commercial bleach (12.7), the reaction failed to take place. However, efficient oxidation occurred when the pH was lowered to 8.3.¹³ The use of a phase-transfer catalyst was unnecessary (Table 1, entry 15). The efficiencies of the reactions were not influenced by the molecular oxygen or nitrogen (Table 1, entry 16). In the absence of TEMPO, the reaction was very sluggish (Table 1, entry 17). In addition, no reaction takes place in the absence of NaClO. When BHT, a well-known radical scavenger, was added to the reaction mixture, the expected benzylic oxidation was inhibited until BHT was consumed, indicating the reaction involves free radical species.¹⁴

The above observations led us to postulate a feasible mechanism for the oxidation (Scheme 2). Benzyl radical was first generated upon TEMPO-induced hydrogen abstraction from the diphenylmethane,¹⁵ which was subsequently converted into benzylcation by Co(III) salts.¹⁶ In the presence of water, benzyl alcohol was formed and then swiftly oxidized to the ketone (path A).¹² Additionally,

Table 1 Optimization of the Reaction Conditions^a


Entry	Cocatalyst	TEMPO (mol%)	NaClO (mmol)	Solvent	Yield (%) ^b
1	none	none	3	CH ₂ Cl ₂	trace
2	none	5	3	CH ₂ Cl ₂	38
3	Co(OAc) ₂	5	3	CH ₂ Cl ₂	95
4	Co(OAc) ₂	1	3	CH ₂ Cl ₂	82
5	Co(OAc) ₂	3	3	CH ₂ Cl ₂	89
6	Co(OAc) ₂	5	1	CH ₂ Cl ₂	73
7	Ni(OAc) ₂	5	3	CH ₂ Cl ₂	93
8	Cu(OAc) ₂	5	3	CH ₂ Cl ₂	56
9	CuCl	5	3	CH ₂ Cl ₂	55
10 ^c	Co(OAc) ₂	5	3	CH ₂ Cl ₂	81
11	Co(OAc) ₂	5	3	EtOAc	72
12	Co(OAc) ₂	5	3	MeCl	90
13	Co(OAc) ₂	5	3	PhCl	95
14	Co(OAc) ₂	5	3	MeCN	70
15 ^d	Co(OAc) ₂	5	3	CH ₂ Cl ₂	96
16 ^e	Co(OAc) ₂	5	3	CH ₂ Cl ₂	93
17	Co(OAc) ₂	none	3	CH ₂ Cl ₂	14

^a All reactions were run in air with diphenylmethane (1.0 mmol), NaClO (3.0 mmol), TEMPO (5 mol%), cocatalyst (1 mol%) in solvent (3 mL) at 0–5 °C for 6 h.

^b Isolated yield.

^c Performed at 25 °C.

^d 5 mol% Bu₄NBr was added.

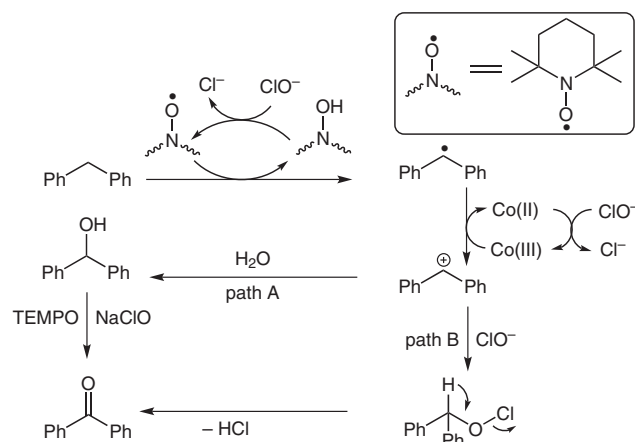
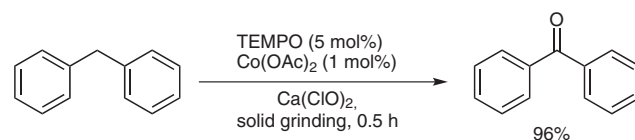
^e Performed under N₂.

when the reaction was performed under solid conditions using Ca(ClO)₂ instead of NaClO, benzophenone could also be obtained with excellent yield (Scheme 3).¹⁷

It was also possible to postulate another pathway involving the attack of ClO⁻ to the benzyl cation and produced alkyl hypochlorite, which then liberated HCl and afforded the ketone (path B).¹⁸ Obviously, path B was also feasible if the reaction was carried out in aqueous NaClO solution. Unexpectedly, benzaldehyde could not be produced from benzyl chloride under the optimized conditions. This fact excluded the stepwise substitution route as an alternative pathway.¹⁹

To investigate the scope and generality of the oxidation method, a wide range of alkylarenes was examined (Table 2).²⁰ It was revealed that the electronic property of substituents on diphenylmethane derivatives displayed lit-

tle effects on the reaction efficiency (Table 2, entries 1–5). Reaction of fluorene (**1f**), which contains two benzene rings, also showed an excellent selectivity (Table 2, entry 6). An interesting fact was observed. For substrates with multibenzyl positions, only one of the benzyl positions was selectively oxidized to give the monooxidation product (Table 2, entries 7 and 8). Methylarenes could be smoothly oxidized to the corresponding aromatic aldehydes (Table 2, entries 9–11). Interestingly, ethylbenzene (**1l**) and isopropylbenzene (**1m**) gave the same product **2l** (Table 2, entries 12 and 13). This evidence strongly indicated that isopropylbenzene might undergo C–C bond cleavage.^{18c,21}

**Scheme 2****Scheme 3**

For substrates containing two available benzylic positions, it was always the one with more substituents that was oxidized with good selectivity due to the higher stability of the radical intermediate (Table 2, entries 14 and 15). 5-Acetyl-11,11-dichloro-5*H*-dibenzo[*b,f*]azepin-10 (11*H*)-one (**2o**) was obtained unexpectedly in the oxidation of **1o** (Table 2, entry 16). It was reasonable to deduce that oxidation of benzylic position produced the monoketone first, then chlorination on α -position of the ketone occurred subsequently.

In conclusion, these results provided a new, catalytic, and direct benzylic C–H oxidation using NaClO/TEMPO/Co(OAc)₂. The readily available reagents and simple workup made the method practical to scale-up²² and therefore useful for manufacturing and commercialization.

Supporting Information for this article is available online at <http://www.thieme-connect.com/ejournals/toc/synlett>.

Table 2 Selective Oxidation of Alkylbenzene Derivatives^a

Entry	Substrate	Selectivity (%) ^b	Product		Yield (%) ^c
1		100		R ¹ = H, R ² = H	2a 95
2 ^d		100		R ¹ = Cl, R ² = H	2b 96
3 ^d		100		R ¹ = Cl, R ² = Cl	2c 81
4 ^d		96		R ¹ = Br, R ² = H	2d 91
5 ^d		95		R ¹ = OMe, R ² = H	2e 87
6 ^e		100			2f 85
7		100			2g 96
8		96			2h 84
9		94		R ³ = H	2i 89
10		90		R ³ = Cl	2j 83
11		92		R ³ = OMe	2k 84
12		100			2l 95
13		97			2l 75
14 ^d		75			2m 64
15 ^d		85			2n 75
16 ^e		100			2o 85

^a Substrate (1.0 mmol), NaClO (3.0 mmol), TEMPO (5 mol%), Co(OAc)₂·4H₂O (1 mol%) in CH₂Cl₂ (3 mL) at 0–5 °C for 6 h.

^b Determined by GC and GC-MS analysis.

^c Isolated yield.

^d 4 mmol of NaClO was employed.

^e 5 mmol of NaClO was employed.

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- (17) **General Procedure for the Oxidation of 1a Using Ca(ClO)₂**
To a mortar were added **1a** (1 mmol), TEMPO (0.05 mmol), Co(OAc)₂ (0.01 mmol), Ca(ClO)₂ (2.5 mmol), and silica gel (0.3 g). After 0.5 h under solid grinding at r.t., the reaction was complete (TLC control). The reaction mixture was dissolved in CH₂Cl₂ (3 mL). After filtration, the solvent was evaporated off. The remaining mixture was passed through a silica gel column to give **2a**. White solid; mp 47.8–49.4 °C. ¹H NMR (400 MHz, CDCl₃): δ = 7.74–7.84 (m, 4 H), 7.53–7.63 (m, 2 H), 7.41–7.52 (m, 4 H). ¹³C NMR (100 MHz, CDCl₃): δ = 196.7, 137.5, 132.3, 130.0, 128.2. MS (EI): *m/z* (%) = 182 (100) [M⁺], 105 (15), 77 (14), 51 (8).
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- (20) **General Procedures**
To a solution of alkylarenes (1 mmol) in CH₂Cl₂ (3 mL) at 0–5 °C, TEMPO (0.05 mmol) and Co(OAc)₂ (0.01 mmol) were added followed by the quick addition of a sample containing 3 mmol of aq NaClO at pH 8.3. After 6 h under magnetic stirring, the reaction was complete (TLC control). The organic phase is separated, washed with H₂O, and dried over Na₂SO₄. After filtration, the solvent was evaporated off. The remaining mixture was passed through a silica gel column to obtain the pure products.
Compound **2o**: pink solid; mp 160.9–162.1 °C. ¹H NMR (400 MHz, CDCl₃): δ = 8.21 (d, *J* = 7.8 Hz, 2 H), 7.39–7.68 (m, 6 H), 2.13 (s, 3 H). ¹³C NMR (100 MHz, CDCl₃): δ = 181.4, 169.9, 141.8, 140.6, 134.4, 133.1, 133.0, 131.5, 130.3, 130.0, 129.0, 128.6, 127.7, 126.3, 89.6, 23.6. MS (EI): *m/z* (%) = 323 (3) [M⁺ + 4], 321 (18) [M⁺ + 2], 319 (27) [M⁺], 284 (64), 242 (100), 213 (95), 178 (71). ESI-HRMS: *m/z* calcd for C₁₆H₁₂Cl₂NO₂: 320.0245; found: 320.0226.
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- (22) **Gramscale Preparation of 2a**
To a solution of **1a** (8.4 g, 50 mmol) in CH₂Cl₂ (150 mL) at 0–5 °C, TEMPO (0.39 g, 2.5 mmol) and Co(OAc)₂ (0.12 g, 0.5 mmol) were added followed by the quick addition of a sample containing 150 mmol of aq NaClO at pH 8.3. The mixture was vigorously stirred for 6 h. The organic phase is separated and washed with H₂O. The solvent was evaporated off. Purification of the residue by recrystallization gave **2a** (7.98 g, 47.5 mmol, mp 47–49 °C) in 95% yield.