

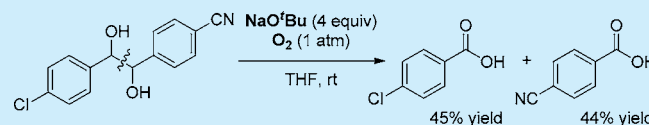
Transition-Metal-Free and Chemoselective NaO^tBu–O₂-Mediated Oxidative Cleavage Reactions of *vic*-1,2-Diols to Carboxylic Acids and Mechanistic Insight into the Reaction Pathways

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S Supporting Information

ABSTRACT: A method for efficient oxidative cleavage of *vic*-1,2-diols using a NaO^tBu–O₂ system resulted in the formation of carboxylic acids in high yields. The present protocol is an eco-friendly alternative to a conventional transition-metal-based method. This new strategy allows large-scale production with nonchromatographic purification while also suppressing competitive reaction pathway such as benzilic acid rearrangement.



The development of transition-metal-free, chemoselective reactions is one of the most important and fundamental tasks in organic synthesis, as it contributes significantly to green chemistry practices.¹ To keep pace with scientific advancement on green processes, we recently reported the transition-metal-free oxidation of primary allylic alcohol to α,β -unsaturated carboxylic acids utilizing NaO^tBu under oxygen atmosphere.^{2a,2} This protocol has distinctive advantages over existing methodologies because it replaces precious transition-metal catalysts (e.g., Au, Pt, Ru, Cu, or Pd), has a lower reaction temperature, and has a shorter reaction time. Transition-metal-free oxidations of a variety of allylic alcohols with high chemoselectivities were fully investigated for the first time.

As part of a wider research program aimed at designing and developing transition-metal-free processes, we became interested in the oxidative cleavage reaction of *vic*-1,2-diol in combination with alkali metal *tert*-butoxide and oxygen.³ In general, the most common oxidizing agents for oxidative cleavage of *vic*-1,2-diols are sodium periodate (NaIO₄), periodic acid (HIO₄), and lead tetraacetate [Pb(OAc)₄], which lead to aldehydes or ketones as major products (Scheme 1, eq 1).⁴ Several different types of oxidants including transition-metal

catalysts also facilitate the direct conversion of *vic*-1,2-diols to carboxylic acids (Scheme 1, eq 2).⁵ For such reactions, either a high oxidation metal–oxo catalyst (i.e., Cr, V, Mn, Ru, W) or a transition metal (Pt) catalyst is still accompanied by high temperature (~70 °C).⁶ In some cases, low product selectivity between aldehydes and carboxylic acids is also observed.^{6b–d}

Recently, a transition-metal-free version of oxidative cleavage of *vic*-1,2-diols to carboxylic acids was reported by utilizing

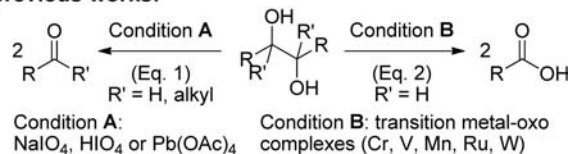
Table 1. Optimization of Reaction Conditions^a

entry	base (equiv)	solvent	time (h)	yield ^b (%)
1		THF	24	ND
2	KO ^t Bu (2)	THF	24	42
3	NaO ^t Bu (2)	THF	24	50
4	NaO ^t Bu (3)	THF	24	56
5	NaO ^t Bu (4)	THF	3	75
6	NaO ⁱ Pr (4)	THF	24	42
7	NaOMe (4)	THF	24	34
8	NaH (4)	THF	24	71
9	KHMDS (4)	THF	24	<5
10	Cs ₂ CO ₃ (4)	THF	24	ND
11	NaO ^t Bu (4)	CH ₂ Cl ₂	3	ND
12	NaO ^t Bu (4)	toluene	3	55
13	NaO ^t Bu (4)	1,4-dioxane	3	54
14	NaO ^t Bu (4)	Et ₂ O	3	64
15	NaO ^t Bu (4)	DMSO	3	67
16 ^c	NaO ^t Bu (4)	THF	3	ND

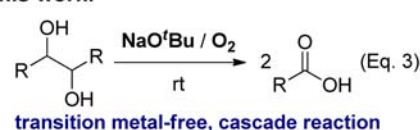
^aGeneral conditions: **1a** (0.5 mmol), base (2–4 equiv), solvent (3 mL), O₂ (1 atm), rt. ^bIsolated yield. ^cAnaerobic conditions.

Scheme 1. Utility of NaO^tBu–O₂ System for Oxidative Cleavage of *vic*-1,2-Diol

previous works:



this work:



Received: April 7, 2014

Published: May 15, 2014

Table 2. Reaction Scope^a

entry	substrate	product	time (h)	yield ^b (%)
1	1a	2a	3	75
2	1b	2b	5	91
3	1c	2c	5	96
4	1d	2d	7	70
5	1e	2e	3	70
6	1f	2f	6	75
7	1g	2g	3.5	89
8	1h	2h	2.5	91
9	1i	2i	2	96
10	1j	2j	5	60
11	1k	2k	5	60
12	1l	1/2 2b + 1/2 2h	2	45 (2b) + 44 (2h)
13 ^c	1m	1/2 2i + 1/2 2m' ^d	8	39 (2i) + 39 (2m')
14	1n	1/2 2b	2	44 (2b)
15 ^e	1o	2o	6	40 ^f

^aGeneral conditions: **1** (0.5 mmol), NaO^tBu (4 equiv), solvent (3 mL), O₂ (1 atm), rt. ^bIsolated yield. ^cUsing NaO^tBu (6 equiv). ^d2m' is *n*-hexanoic acid. ^eUsing NaO^tBu (6 equiv). ^fDetermination of the yield by Fisher esterification with H₂SO₄-MeOH.

organocatalysis [nitroxyl radical as organocatalyst and PhI(OAc)₂ (5 equiv)/or NaClO₂ (3 equiv) as oxidants], photooxidation [2-chloroanthraquinone as catalyst, O₂, *hν* (400-W Hg lamp)], aqueous sodium hypochlorite (10 equiv), hydroperoxide [*tert*-butyl hydroperoxide (4 equiv), KO^tBu (3

equiv), 80 °C], and sodium perborate [NaBO₃·4H₂O (10 equiv) as oxidant in AcOH (2–3 mL per oxidant) under reflux conditions].⁷ Therefore, multifarious ways to accomplish oxidative cleavage of *vic*-1,2-diols into carboxylic acids without the need for transition-metal catalysts, costly oxidants, and power supply instruments are highly desirable.

Herein, we report a scalable, transition-metal-free, and chemoselective cascade of reactions utilizing NaO^tBu and O₂ as oxidant, which are both readily available and inexpensive. This could potentially address the shortcomings of the aforementioned transition metal-based methodologies (Scheme 1, eq 3). The labeling experiment with ¹⁸O₂ was performed to elucidate the pathway for the preferential mechanism.

To investigate the viability of the envisioned direct oxidative cleavage reaction of *vic*-1,2-diol, hydrobenzoin **1a** was selected as a model substrate. First, various bases and solvents were screened. The results are summarized in Table 1. In a controlled experiment it was found that the reaction did not proceed in the absence of either base or oxygen as oxidant (Table 1, entries 1 and 16).

The use of NaO^tBu gave a slightly better chemical yield than the use of KO^tBu (Table 1, entries 2 and 3). Product yield was significantly influenced by varying the equivalents of NaO^tBu (Table 1, entries 3–5). The influence of the alkoxide nature was also examined. For instance, sodium isopropoxide and sodium methoxide gave low product yield (Table 1, entries 6–7). Interestingly, the chemical yield of product increased in the following order of alkoxide ion basicity: *tert*-butoxide > isopropoxide > methoxide. NaH gave results comparable to those obtained from reaction mediated by NaO^tBu, but a much longer reaction time (24 h) was required (Table 1, entry 8). However, KHMDS and Cs₂CO₃ showed negligible conversion. A number of other solvents, including CH₂Cl₂, toluene, 1,4-dioxane, Et₂O, and DMSO, were subsequently investigated, but they were inferior to THF in terms of yield (Table 1, entries 11–15).

We next explored the scope of this reaction of *vic*-1,2-diols with NaO^tBu under optimized conditions [NaO^tBu (4 equiv), O₂ (1 atm), THF, rt]. The results are summarized in Table 2. A

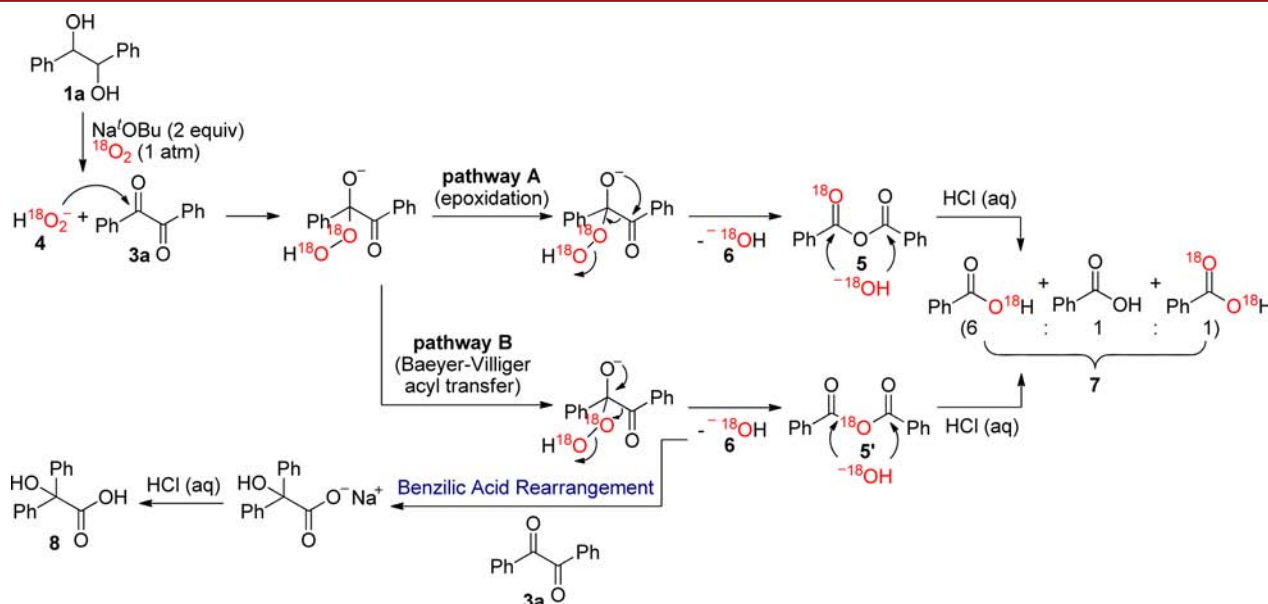


Figure 1. Proposed mechanism for the oxidative cleavage of *vic*-1,2-diols to carboxylic acids.

series of symmetrical and unsymmetrical *vic*-1,2-diols were examined. In general, the symmetrical *vic*-1,2-diols bearing electron-withdrawing substituents smoothly transformed to corresponding products in high yields ranging from 70% to 96%. However, those with electron-donating substituents resulted in relatively lower yields (60%). Interestingly, unsymmetrical *vic*-1,2-diols (**1l** and **1m**) can be oxidatively cleaved with NaO^tBu-O₂ to form two different acids (Table 2, entries 12 and 13). Specifically, 4-chlorobenzoic acid **2b** and 4-cyanobenzoic acid **2h** were obtained in virtually identical yields (~45%) when hydrobenzoin derivative **1l** was employed. Unsymmetrical *vic*-1,2-diol bearing both aryl and alkyl substituents also gave the corresponding products (**2i** and **2m'**).

Styrene-derived terminal 1,2-diol **1n** gave one-half the product **2b** with 44% yield (Table 2, entry 14). Aliphatic internal 1,2-diol **1o** proved suitable candidate for this transformation. The yield of actual product **2o** was determined by Fischer esterification of the resulting 5-phenylpentanoic acid with MeOH in the presence of catalytic amounts of H₂SO₄ (Table 2, entry 15). During the oxidative cleavage reaction of *vic*-1,2-diol, small amounts of benzoic acid (10%) were detected in most cases.

To ascertain mechanistic insights into the nature of oxidant, an ¹⁸O isotopic labeling experiment was conducted with ¹⁸O₂ gas (Figure 1).

Double deprotonation of the hydroxyl group in *vic*-1,2-diol with 2 equiv of NaO^tBu presumably generated 1,2-diketone **3** and ¹⁸O-labeled hydroperoxide anion **4** via hydride transfer from the α -carbon of alcohol to the ¹⁸O-labeled oxygen. The subsequent nucleophilic attack of ¹⁸O-labeled hydroperoxide anion **4** to the carbonyl group of 1,2-diketone would form two different ¹⁸O-labeled anhydride **5** and **5'** as transient intermediate and ¹⁸O-labeled hydroxide ion **6** via epoxidation mechanism (pathway A) or Baeyer–Villiger mechanism with acyl group migration (pathway B), leading to three main categories of carboxylic acids **7** after simple acid-workup.⁸ The resulting products were subjected to GC/MS analysis (Hewlett-Packard Agilent 6890, 5973 MSD). The ¹⁶O and ¹⁸O compositions of individual carboxylic acids were determined by the relative abundances of mass peaks at $m/z = 122$ for ¹⁶O¹⁶O, $m/z = 124$ for ¹⁶O¹⁸O, and $m/z = 126$ for ¹⁸O¹⁸O.

As shown in Figure 2 and proposed in Figure 1, it was revealed that the relative abundances of isotopic masses for each product **7** are identical to those of isotopic masses [theoretical ratio of benzoic acid isotopes [¹⁶O¹⁶O:¹⁶O¹⁸O:¹⁸O¹⁸O] = 1:6:1, experimental ratio of [¹⁶O¹⁶O:¹⁶O¹⁸O:¹⁸O¹⁸O] = 1:6.2:1.3).

During the reaction course, small amounts of benzoic acid derivative **8** were observed. This indicates that the released hydroxide ion **6** serves as a formidable competitor to the formation of carboxylic acid **7** and α -hydroxy acid **8**. Namely, the benzoic acid rearrangement had clearly occurred, in which 1,2-diketone **3** was converted to α -hydroxy acid **8** upon treatment with hydroxide ion **6**. This information provides crucial evidence of the existence of 1,2-diketone and hydroxide ion while allowing a better understanding of the reaction mechanism.

To verify the existence of 1,2-diketone, a reaction of 4,4'-methoxyhydrobenzoin **1k** was carried out with 4 equiv of NaO^tBu under oxygen atmosphere at -20 °C to produce 4,4'-methoxybenzil **3k** in 11% yield. The product was identified by ¹H and ¹³C NMR spectroscopy. Despite being hampered by

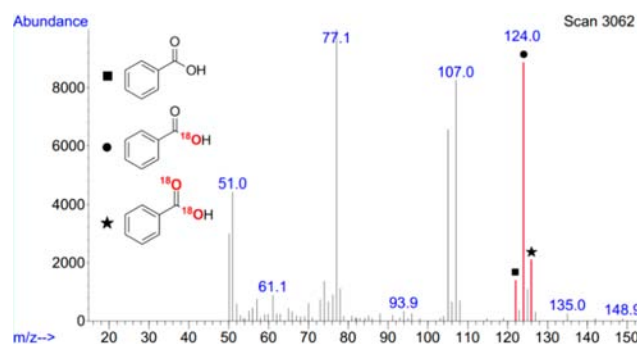
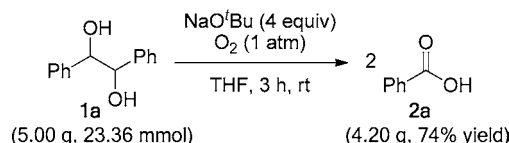
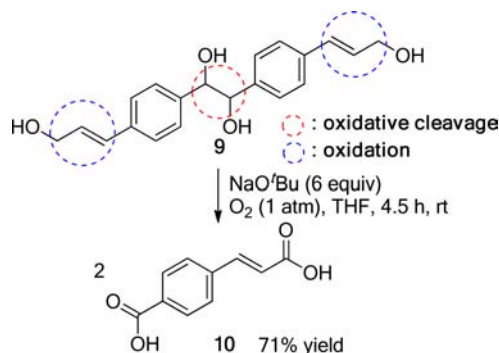


Figure 2. Isotopic labeling results from the oxidative cleavage of *vic*-1,2-diol utilizing a NaO^tBu-¹⁸O₂ system.

Scheme 2. Large-Scale Production of **2a**



Scheme 3. Transition-Metal-Free, Oxidation/Oxidative Cleavage Reaction in a One-Pot Manner Utilizing a NaO^tBu-O₂ System



parasitic pathways, such as benzoic acid rearrangement, the desired carboxylic acid was almost selectively formed. The existence of reactive intermediate such as anhydride **5** or **5'**, which are not easily isolable from reaction mixture in the presence of strong nucleophile (such as hydroxide ion⁹), offers the possibility to suppress competing parasitic reactions (benzoic acid rearrangement). The ability to control selectivity while avoiding the use of transition-metal catalyst is one of the most distinctive features of the oxidative cleavage of *vic*-1,2-diols. The presence of trace transition metal elements in NaO^tBu was also examined by ICP-ACE, and the results are shown in ref 10.

A 23-fold scale-up was also demonstrated with substrate **1a** compared to the currently approved reaction under the NaO^tBu-O₂ system. The detailed experimental procedure is described in the Supporting Information. Organic and aqueous layers were clearly separated by salting-out, eliminating the need for additional organic extraction. Moreover, the desired product **2a** was easily isolated from residues due to the insolubility of resulting side product benzoic acid **8** in EtOAc/hexanes (Scheme 2).

Finally, the oxidation/oxidative cleavage reaction of **9** was performed in a one-pot manner. For example, a simple primary allylic alcohol moiety was oxidized to α,β -unsaturated

carboxylic acid, and a 1,2-diol moiety was oxidatively cleaved to carboxylic acid (Scheme 3).

In summary, we have developed a transition-metal-free, oxidative cleavage reaction of *vic*-1,2-diols to carboxylic acids with NaO^tBu under oxygen atmosphere. We also demonstrated how to scale-up experiments without organic extraction and chromatographic technique. This protocol was used to perform an oxidation/oxidative cleavage reaction in a one-pot fashion.

■ ASSOCIATED CONTENT

■ Supporting Information

General experimental procedure and characterization of all compounds are provided. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Author Contributions

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the NRF Nano·Material Technology Development Program (2012M3A7B4049652) and the KETEP Human Resources Development Program (20124010203270).

■ REFERENCES

- (1) Andersson, P. G.; Munslow, I. J. *Modern Reduction Method*; Wiley-VCH: New York, 2008.
- (2) For allylic alcohol oxidation utilizing a NaO^tBu-O₂ system, see: (a) Kim, S. M.; Kim, Y. S.; Kim, D. W.; Yang, J. W. *Green Chem.* **2012**, *14*, 2996. For representative examples of coupling reactions using alkali *tert*-butoxide, see: (b) Sun, C.-L.; Li, H.; Yu, D.-G.; Yu, M.; Zhou, X.; Lu, X.-Y.; Huang, K.; Zheng, S.-F.; Li, B.-J.; Shi, Z.-J. *Nat. Chem.* **2010**, *2*, 1044. (c) Shirakawa, E.; Itoh, K.-i.; Higashino, T.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 15537. (d) Liu, W.; Cao, H.; Zhang, H.; Zhang, H.; Chung, K. H.; He, C.; Wang, H.; Kwong, F. Y.; Lei, A. *J. Am. Chem. Soc.* **2010**, *132*, 16737. (e) Studer, A.; Curran, D. P. *Angew. Chem., Int. Ed.* **2011**, *50*, 5018. (f) A, S.; Liu, X.; Li, H.; He, C.; Mu, Y. *Asian J. Org. Chem.* **2013**, *2*, 857.
- (3) For transition-metal-free, aerobic oxidative cleavage reactions of α -hydroxyl ketones with alkyl halides to esters using K₂CO₃, see: Liu, H.; Dong, C.; Zhang, Z.; Wu, P.; Jiang, X. *Angew. Chem., Int. Ed.* **2012**, *51*, 12570.
- (4) (a) Fieser, L. F.; Fieser, M. In *Reagents for Organic Synthesis*; Wiley-VCH: New York, 1967; p 815. (b) Shing, T. K. M. In *Comprehensive Organic Synthesis*; Trost, B. M., Eds.; Pergamon Press: Oxford, 1991; p 703.
- (5) (a) Sugimoto, H.; Spencer, L.; Sawyer, D. T. *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 1731. (b) Dakdouki, S. C.; Villemin, D.; Bar, N. *Eur. J. Org. Chem.* **2011**, 4448. (c) Du, G.; Ellern, A.; Woo, L. K. *Inorg. Chem.* **2004**, *43*, 2379. (d) Okamoto, T.; Sasaki, K.; Oka, S. *J. Am. Chem. Soc.* **1988**, *110*, 1187. (e) Beebe, T. R.; Hii, P.; Reinking, P. *J. Org. Chem.* **1981**, *46*, 1927. (f) Zhong, Y.-L.; Shing, T. K. M. *J. Org. Chem.* **1997**, *62*, 2622. (g) Marken, F.; Squires, A. M.; Alden, J. A.; Compton, R. G.; Buston, J. E. H.; Moloney, M. G. *J. Phys. Chem. B* **1998**, *102*, 1186. (h) Cambie, R. C.; Chambers, D.; Rutledge, P. S.; Woodgate, P. D. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1483.
- (6) (a) Bailey, A. J.; Griffith, W. P.; Mostafa, S. I.; Sherwood, P. A. *Inorg. Chem.* **1993**, *32*, 268. (b) Ait-Mohand, S.; Levina, A.; Lunak, S.; Muzart, J. *Inorg. Chim. Acta* **1995**, *238*, 183. (c) Tsang, S. C.; Zhu, J.;

Steele, A. M.; Meric, P. *J. Catal.* **2004**, *226*, 435. (d) Barroso, S.; Blay, G.; Fernández, I.; Pedro, J. R.; Ruiz-García, R.; Pardo, E.; Lloret, F.; Muñoz, M. C. *J. Mol. Catal. A: Chem.* **2006**, *243*, 214. (e) Che, C.-M.; Yip, W.-P.; Yu, W.-Y. *Chem.—Asian J.* **2006**, *1*, 453. (f) Fujitani, K.; Mizutani, T.; Oida, T.; Kawase, T. *J. Oleo Sci.* **2009**, *58*, 323. (g) Alagiri, K.; Prabhu, K. R. *Tetrahedron* **2011**, *67*, 8544. (h) Schmidt, A.-K. C.; Stark, C. B. W. *Org. Lett.* **2011**, *13*, 5788.

(7) (a) Shibuya, M.; Doi, R.; Shibuta, T.; Uesugi, S.-i.; Iwabuchi, Y. *Org. Lett.* **2012**, *14*, 5006. (b) Shibuya, M.; Shibuta, T.; Fukuda, H.; Iwabuchi, Y. *Org. Lett.* **2012**, *14*, 5010. (c) Matsusaki, Y.; Yamaguchi, T.; Tada, N.; Miura, T.; Itoh, A. *Synlett* **2012**, 23, 2059. (d) Shaikh, T. M.; Hong, F.-E. *Tetrahedron* **2013**, *69*, 8929. (e) Khurana, J. M.; Sharma, P.; Gogia, A.; Kandpal, B. M. *Org. Prep. Proced. Int.* **2007**, *39*, 185. (f) Banerjee, A.; Hazra, B.; Bhattacharya, A.; Banerjee, S.; Banerjee, G. C.; Sengupta, S. *Synthesis* **1989**, 765.

(8) Cullis, P. M.; Arnold, J. R. P.; Clarke, M.; Howell, R.; DeMira, M.; Naylor, M.; Nicholls, D. *J. Chem. Soc., Chem. Commun.* **1987**, 1088.

(9) The reaction of **1a** was performed in the presence of TEMPO (1–3 equiv) as radical scavenger under optimal conditions, resulted in the formation of the desired product **2a** in high yield. It is crucial evidence to support the involvement of non-free-radical species (e.g., [•]OH, [•]O₂H) in this transformation.

(10) In order to eliminate the possibility of the presence of trace transition-metal elements in NaO^tBu that would potentially affect our results, we purified the NaO^tBu by sublimation and also examined by inductively coupled plasma-atomic emission spectrometry (ICP-AES) prior to our investigation. These results clearly show that the contents of transition metals (Pd, Fe, and Cu) were in the range of 0.2–0.5 ppm. After identifying negligible transition metal contents, we carried out the reaction of **1a** with the purified NaO^tBu under oxygen atmosphere to produce the desired product **2a** in a yield similar to that obtained in Table 2.

■ NOTE ADDED AFTER ASAP PUBLICATION

A partially corrected version of this article published May 15, 2014. The fully corrected version was reposted on May 16, 2014.