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Oxacycle Synthesis via Intramolecular Reaction of Carbanions and Peroxides

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S *Supporting Information*

ABSTRACT: The intramolecular reaction of dialkyl peroxides with carbanions, generated via chemoselective metal-heteroatom exchange or deprotonation, provides a new approach to cyclic ethers. Applied in tandem with C−C bond formation, the strategy enables a one-step annelation to form oxaospirocycles.

Ethers, which comprise critical substructures in many bioactive molecules and natural products,[1] are typically synthesized through attack of nucleophilic oxygen on an electrophilic carbon.[1,2] The converse of this strategy, attack of a carbanion on electrophilic oxygen, has been investigated to only a limited extent for intermolecular reactions and is essentially unexplored for intramolecular reactions. We now demonstrate that chemoselective generation of carbanions in the presence of appropriately positioned O−O bonds of dialkyl peroxides allows the efficient introduction of cyclic ethers (Figure 1), including frameworks (for example, **15a** or **19b**, vide infra) challenging to approach via existing methodology.

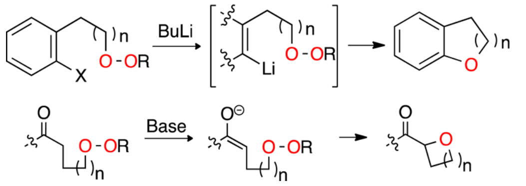
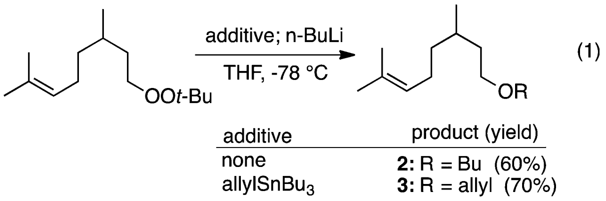


Figure 1. Overview of oxacycle synthesis via reactions of peroxides and carbanions.

Previous reports have described the intermolecular reaction of simple organometallics with dialkyl peroxides,[3] peresters,[4] and endoperoxides.[5] Bissilyl peroxides and lithiated hydroperoxides have been applied to oxygenation of lithiated arenes and alkenes.[6,7] However, the only precedent for the corresponding *intra*molecular reactions of carbanions with peroxides is the 3-*exo* cyclization of short-lived enolate intermediates formed during nucleophilic epoxidation reactions.[8]

At the outset of these studies, we faced two major uncertainties: first, would it be possible to generate reactive carbanions in the presence of a peroxide; and, second, would the carbanion/peroxide pair undergo intramolecular C−O bond formation. The question of chemoselective generation of an organolithium nucleophile was initially investigated using a dialkyl peroxide (**1**) derived from reaction of *t*-butyl hydroperoxide with dihydrogeraniol methanesulfonate.[9] Consistent with previous observations,[3a] reaction of **1** with *n*-BuLi proceeded readily to furnish butyl ether **2** (eq 1). Repeating this reaction in the presence of a slight excess of allyl tributylstannane resulted in predominant formation of the allyl ether (**3**), demonstrating that Li/heteroatom exchange proceeds much more rapidly than C−O bond formation.



additive	product (yield)
none	**2:** R = Bu (60%)
allylSnBu$_3$	**3:** R = allyl (70%)

Confident of our ability to selectively generate a carbanion in the presence of a peroxide, we prepared a family of substrates (**6a**−**c** and **9**) incorporating a dialkyl peroxide and a precursor aryllithium precursor (Scheme 1). The peroxide was either installed via displacement of a sulfonate (base) or iodide (Ag_2O).[10] The lower yield for phenethyl peroxide **9** reflects a tendency for Kornblum elimination in this skeleton.[11]

Scheme 1. Synthesis of Aryl Peroxide Substrates

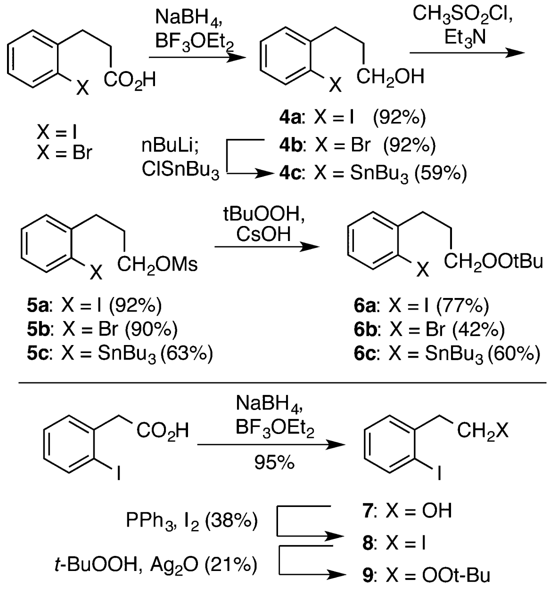


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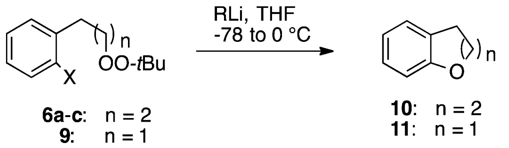
Table 1 illustrates the results of metal-heteroatom exchange for peroxides **6a**–**c** and **9**. Addition of either *n*-BuLi or PhLi to a–78 °C solution of **6a** (iodide) or **6b** (bromide), followed by warming of the reaction mixture to 0 °C, afforded good yields of dihydrobenzopyran **10**. The corresponding reactions of the tributylstannyl arene (**6c**) proceeded in much lower yield (PhLi) or essentially not at all (BuLi). Lithiation of *o*-iodophenethyl peroxide **9** furnished dihydrobenzofuran in excellent yield.

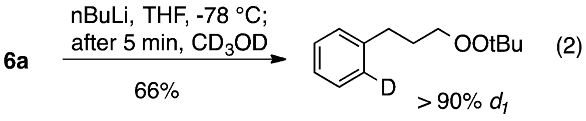
Table 1. Lithiation/Cyclization



subst	*n*	X	prod	R	yield (%)[a]
6a	2	I	**9**	*n*-Bu	71
6a	2	I	**9**	Ph	73
6b	2	Br	**9**	*n*-Bu	71
6b	2	Br	**9**	Ph	47
6c	2	$SnBu_3$	**9**	*n*-Bu	trace
6c	2	$SnBu_3$	**9**	Ph	19
9	1	I	**10**	*n*-Bu	90(58)[b]

[a]GC yields. [b]Isolated yield.

Repeating the lithiation of **6a** and quenching the reaction with MeOH-d_4 prior to warming resulted in formation of a monodeuterated peroxide (eq 2), demonstrating that lithiation occurs more rapidly and at lower temperature than intramolecular C–O bond formation.



We next investigated corresponding cyclizations of enolate anions, prepared as illustrated in Scheme 2.

Conditions for cyclization were initially investigated for the 5-*exo* closure of peroxide **14b** (Table 2). The reaction, which generates *tert*-butoxide anion as a byproduct, proceeded rapidly in THF in the presence of KOtBu or KH. Only traces of products were observed using LDA.

Scheme 2. Synthesis of Peroxyketones

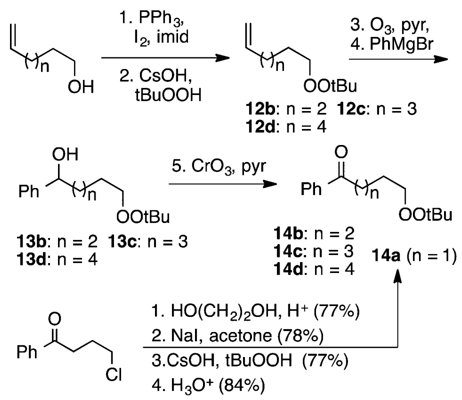
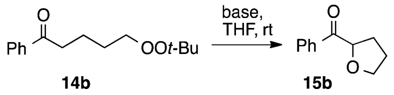


Table 2. Investigation of Cyclization Conditions

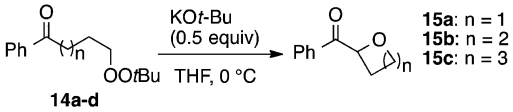


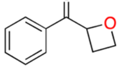
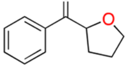
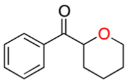
base	equiv	isolated yield
KO*t*-Bu	0.5	81% (99)[a]
KO*t*-Bu	1.0	85%
KO*t*-Bu	2.0[b]	88%[b]
KH	1.0	86% (99)[a]
KH	2.0	89%
LDA	1.0	NR

[a]GC yields. [b]The use of greater amounts of KOtBu resulted in formation of products derived from peroxide decomposition.[11]

Application of the KO*t*-Bu conditions to the cyclization of **14a**–**c** furnished good yields of the oxetane, tetrahydrofuran, and tetrahydropyran (Table 3). Peroxide **14d** failed to undergo 7-*exo* closure to the oxepane, instead slowly undergoing decomposition.[11]

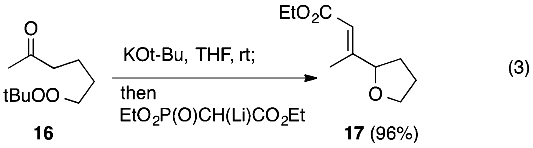
Table 3. Intramolecular C–O Formation



reactant	n	product	yield
14a	1	**15a** 	70%
14b	2	**15b** 	81% (99)[a]
14c	3	**15c** 	80
14d	4	slow decomposition	-

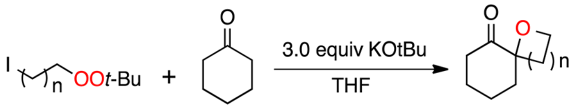
[a]GC yield.

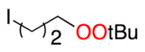
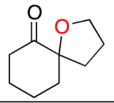
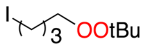
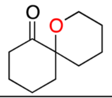
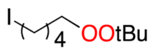
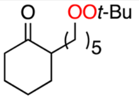
The transformation was not limited to aryl ketones, as evidenced by cyclization of peroxyhexanone **16** (eq 3); the volatile product was isolated after homologation with a Horner–Emmons reagent.



Finally, we investigated the reaction of enolates with a series of *t*-butyl iodoalkyl peroxides **18a**–**d**, available in one step from the corresponding 1,*n*-dihalides (Table 4). The results demonstrate the ability to achieve, in one step, a high-yielding annelation of spirocyclic ethers onto ketone frameworks, opening the door to a class of spirocycles previously approachable mainly through cationic ring expansions.[12] The isolation of the homologated peroxide (**20**) during attempted formation of a 7-membered ring provides strong evidence that the formation of the 5- and 6-membered spirocycle proceeds via initial formation of a C–C bond.

Table 4. Formation of Spirocyclic Ethers via Tandem C−C and C−O Bond Formation



reactant	product	yield
18a 	**19a** 	86 %
18b 	**19b** 	87 %
18d 	**20** 	74 %

In conclusion, we have demonstrated the chemoselective generation of carbanions in the presence of dialkyl peroxides and the application of the resulting intermediates to establish new C−O bonds. This alternative to more traditional etherifications provides a new approach to synthesis of spirocyclic ethers, aryl ethers, and various oxacycles including oxetanes.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, spectral listings, and selected ^{1}H and ^{13}C NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Forsyth, C. J., Ed. *Science of Synthesis, v. 27: Ethers*; George Thieme Verlag: Stuttgart, 2008.

(2) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852−860. Torraca, K.; Huang, X.; Parrish, C.; Buchwald, S. *J. Am. Chem. Soc.* **2001**, *123*, 10770−10771. Gowrisankar, S.; Sergeev, A. G.; Anbarasan, P.; Spannenberg, A.; Neumann, H.; Beller, M. *J. Am. Chem. Soc.* **2010**, *132*, 11592−11598. Winternheimer, D. J.; Shade, R. E.; Merlic, C. A. *Synthesis* **2010**, 2497−2511. Naidu, A. B.; Jaseer, E. A.; Sekar, G. *J. Org. Chem.* **2009**, *74*, 3675−3679. Larrosa, I.; Romea, P.; Urpí, F. *Tetrahedron* **2008**, *64*, 2683−2723.

(3) Dialkyl peroxides: (a) Baramki, G. A.; Chang, H. S.; Edward, J. T. *Can. J. Chem.* **1962**, *40*, 441−445. (b) Hou, Y.; Meyers, C. Y.; Akomeah, M. *J. Org. Chem.* **2009**, *74*, 6362−6364.

(4) Peresters: Lawesson, S.-O.; Yang, N. C. *J. Am. Chem. Soc.* **1959**, *81*, 4230−4233.

(5) Endoperoxides: (a) Schwaebe, M.; Little, R. D. *Tetrahedron Lett.* **1996**, *37*, 6635−6638. (b) Ziegert, E.; Bräse, S. *Synlett* **2006**, 2119−2123.

(6) Taddei, M.; Ricci, A. *Synthesis* **1986**, 633−635. Dembech, P.; Ricci, A.; Seconi, G.; Taddei, M. *Org. Synth.* **1997**, *74*, 84. Davis, F. A.; Lai, G. S.; Wei, J. *Tetrahedron Lett.* **1988**, *29*, 4269−4272.

(7) Panek, E. J.; Kaiser, L. R.; Whitesides, G. M. *J. Am. Chem. Soc.* **1977**, *99*, 3708−13.

(8) Meth-Cohn, O.; Moore, C.; Taljaard, H. C. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2663−2674. Porter, M.; Skidmore, J. *Org. React.* **2009**, *74*, 425−672.

(9) Kyasa, S.; Puffer, B. W.; Dussault, P. H. *J. Org. Chem.* **2013**, *78*, 3452−3456 and references within.

(10) Kim, H.-S.; Nagai, Y.; Ono, K.; Begum, K.; Wataya, Y.; Hamada, Y.; Tsuchiya, K.; Masuyama, A.; Nojima, N.; McCullough, K. J. *J. Med. Chem.* **2001**, *44*, 2357−2361. Bloodworth, A. J.; Eggelte, H. J. *J. Chem. Soc., Perkin Trans. 1* **1981**, 3272−3278.

(11) The isolated byproduct resulted from intramolecular attack of the enolate on an aldehyde formed via E_1CB fragmentation of the peroxid: Kornblum, N.; DeLaMare, H. E. *J. Am. Chem. Soc.* **1951**, *73*, 880−881.

(12) Rosenberg, S.; Leino, R. *Synthesis* **2009**, 2651−2673. Paquette, L. A.; Negri, J. T.; Rogers, R. D. *J. Org. Chem.* **1992**, *57*, 3956−3965. Zhang, Q.-W.; Fan, C.-A.; Zhang, H.-J.; Tu, Y.-Q.; Zhao, Y.-M.; Gu, P.; Chen, Z.-M. *Angew. Chem., Int. Ed.* **2009**, *48*, 8572−8574.