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Type 1 Ring-Opening Reactions of Cyclopropanated 7-Oxabenzonorbornadienes with Organocuprates

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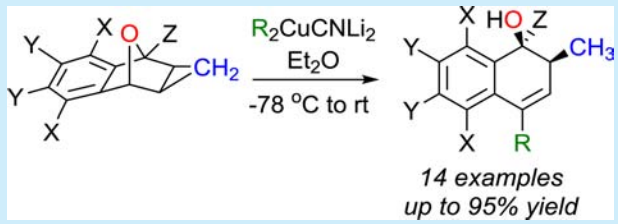
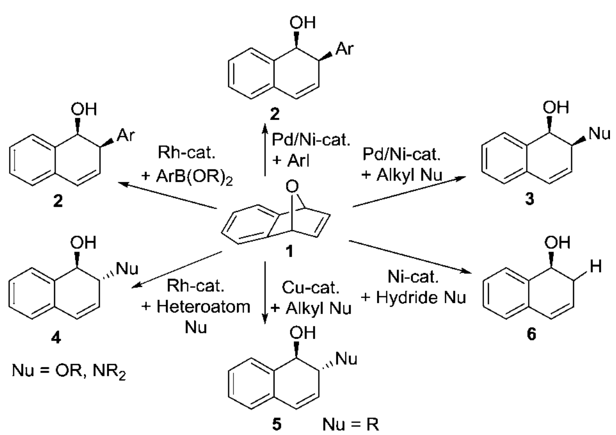
Supporting Information

ABSTRACT: For the first time, nucleophilic ring-openings of cyclopropanated 7-oxabenzonorbornadiene were investigated, providing a novel approach to the preparation of 2-methyl-1,2-dihydronaphthalen-1-ols. Satisfactory yields (up to 95%) were achieved using n-$Bu_2CuCNLi_2$ as the nucleophile and Et_2O as the solvent. The reaction demonstrated successful incorporation of primary, secondary, tertiary and aromatic nucleophiles, as well as ring-openings of substrates bearing arene substituents and C1-bridgehead substituents. A generalized mechanism for these transformations is also proposed.



Heterobicyclic alkenes serve as valuable precursors for the creation of highly substituted cyclic and acyclic systems alike.[1] Most notably, ring-opening reactions of oxabicyclic alkenes are well recognized for their ability to generate multiple stereocenters in a single step.[2] Nucleophilic ring-openings of 7-oxabenzonorbornadiene **1** provide a diverse supply of 2-substituted dihydronaphthalenol derivatives, depending on the metal catalyst and nucleophile employed (Scheme 1).[3]

Scheme 1. Transition-Metal-Catalyzed Nucleophilic Ring-Opening Reactions of 7-Oxabenzonorbornadiene 1

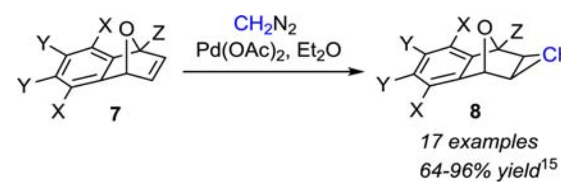


Syn-stereoisomeric products **2** or **3** are attained when rhodium,[4] palladium,[5] or nickel[6] are supplied with an arene nucleophile and when palladium[7] or nickel[8] catalyzes the addition of an alkyl nucleophile. In contrast, the *anti*-diastereomers **4** or **5** are obtained when rhodium assists addition of a heteroatomic nucleophile[9] or when copper catalyzes addition of an alkyl nucleophile.[10] Furthermore, reductive openings of **1** with hydride nucleophiles have also been achieved to provide the unsubstituted **6**.[11] The resulting dihydronaphthalenols **2**−**6** and their variously substituted analogues find broad application in the synthesis of biologically active substances, such as arnottin I,[12] as well as medicinal compounds, such as sertraline.[13]

While nucleophilic ring-openings of olefin **1** have been extensively studied, the similar chemical reactivities reported between olefins and cyclopropanes[14] drew our attention to nucleophilic ring-opening reactions for cyclopropanated analogues of **1**. To begin our work, the substrates were prepared by cyclopropanation of **7** using *in situ* generated diazomethane, giving **8** in moderate to excellent yields (Scheme 2).[15] For purposes of optimization, early trials focused on reactions involving the unsubstituted parent compound **8a** (Scheme 3).

Three outcomes could be envisioned for nucleophilic ring-opening reactions of **8a**, based on the position of the attacking nucleophile and the bond being broken (Scheme 3). The first type of reaction would invoke nucleophilic attack at bridgehead position C1 (Scheme 3), with simultaneous cleavage of the C−

Scheme 2. Recent Preparations of Cyclopropanated 7-Oxabenzonorbornadienes



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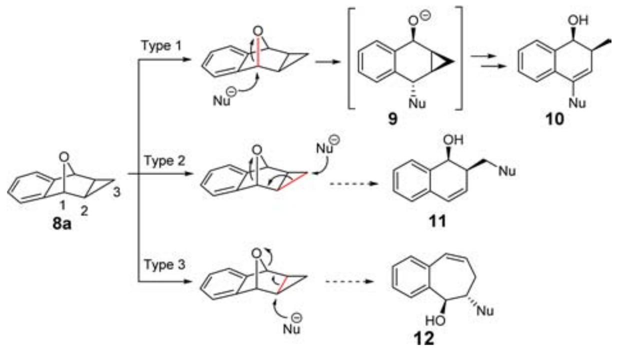
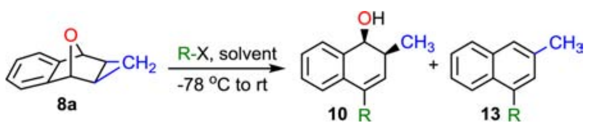
Scheme 3. Proposed Types of Ring-Opening Reactions for Cyclopropanated 7-Oxabenzonorbornadienes



O bond to give the ring-opened product **9**. Early experiments, however, showed that **9** was in fact not isolable, but further undergoes ring-opening of the cyclopropane, leading to the formation of dihydronaphthalenol **10** upon aqueous work up (*vide infra*).[16] This class of peculiar reactions which produced **10** was given the name Type 1 ring-opening reactions. To the best of our knowledge, this paper describes the first account where a cyclopropanated heterobicyclic molecule **8a** has been opened in this fashion. The second type of conceivable reaction would result from nucleophilic attack on the cyclopropane at position C3 (Scheme 3), leading to the ring-opened product **11**. The third type of potential reaction would involve nucleophilic attack at the cyclopropane position C2 (Scheme 3), producing cycloheptenol derivative **12** through ring expansion.

The effects of organometallic nucleophile, solvent, and reaction time on Type 1 nucleophilic ring-openings of **8a** are summarized in Table 1. Initial attempts using Grignard reagent as the organometallic nucleophile were futile, with no improvement seen with increased temperatures (Table 1, entries 1 and 2). Using organolithium reagent,[17a] however, the ring-opened product **10** was obtained as the sole product in 20% yield; again, no appreciable temperature dependence was noted (entries 3 and 4). Other organometallic reagents including *in situ* generated organocerium (entry 5)[17b] and Lewis acidic monoorganocopper (entry 6)[18] compounds were less effective or showed no conversion at all. It was not until subsequent trials involving organocuprates were attempted that an increase in effectiveness was seen: Gilman reagents[18,19] generated from copper(I) halide salts showed that chloride and bromide derivatives were more effective than the iodide derivative, giving **10** in moderate yields of >55% after 8 h (entries 7–9). It was at this time that the formation of an aromatic side product **13** was first noted. Higher-order cuprates,[20] when subjected to the reaction, also gave promising yields of **10** with small proportions of **13** (entries 10 and 11). Finally, a range of solvents was screened. The choice of diethyl ether drastically improved the yield of **10** to near-quantitative conversion (entry 12), while reactions in toluene, hexanes, and dichloromethane proved to be unsuccessful (entries 13–15). The structures of these compounds were determined by various NMR experiments (^{1}H, ^{13}C, HSQC, and GOESY)[21] and were compared with the data of a structurally analogous *syn*-2-methyl-1,2-dihydronaphthalen-1-ol (R = H) from the literature.[22] With the optimization complete, the combination of higher order cyanocuprate in diethyl ether was selected for investigations toward the reaction scope.

Table 1. Organometallic Reagent and Solvent Effects on Type 1 Ring-Opening Reactions of 8a

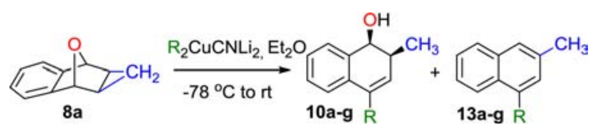


entry	organometallic reagent	solvent	time (h)	8a (%)[a]	10 (%)[a]	13 (%)[a]
1	EtMgBr	THF	72	94	0	0
2[b]	EtMgBr	THF	72	86	0	0
3	*n*-BuLi	THF	72	76	20	0
4[b]	*n*-BuLi	THF	72	72	21	0
5	*n*-BuCeCl$_2$	THF	24	91	4	0
6	*n*-BuCu·BF$_3$	THF	72	92	0	0
7	*n*-Bu$_2$CuLi·LiI	THF	8	65	30	2
8	*n*-Bu$_2$CuLi·LiBr	THF	8	22	67	2
9	*n*-Bu$_2$CuLi·LiCl	THF	8	35	58	2
10	*n*-Bu$_3$CuLi$_2$·LiCl	THF	8	20	71	3
11	*n*-Bu$_2$CuCNLi$_2$	THF	8	29	69	2
12	*n*-Bu$_2$CuCNLi$_2$	Et$_2$O	8	2	95	2
13	*n*-Bu$_2$CuCNLi$_2$	toluene	8	91	0	0
14	*n*-Bu$_2$CuCNLi$_2$	hexanes	8	96	0	0
15	*n*-Bu$_2$CuCNLi$_2$	DCM	8	95	0	0

[a]Isolated yield after column chromatography. [b]Reaction was heated to 60–65 °C.

The scope of the ring-opening reactions of **8a** using various higher order cyanocuprate nucleophiles is shown in Table 2.

Table 2. Effects of Various Organocuprate Nucleophiles on Type 1 Ring-Opening Reactions of 8a



entry	nucleophile	time (h)	8a (%)[a]	10 (%)[a]	13 (%)[a]
1	*n*-Bu	8	2	95	2
2	Me	160	40	59	0
3[b]	Me	48	16	64	19
4	Et	16	48	50	2
5	Et	120	49	10	28
6	Et	160	15	10	64
7	Hex	30	35	40	1
8	Hex	140	0	18	77
9	*i*-Pr	40	3	45	47
10	*t*-Bu	30	37	12	20
11	Ph	48	60	23	0

[a]Isolated yield after column chromatography. [b]10 equiv of organocuprate, heated to 65–75 °C.

Compared to *n*-Bu (entry 1), the methyl nucleophile (entry 2) was particularly unreactive, resulting in a 40% recovery of **8a** after one week. This likely resulted from the low transferability of a methyl ligand relative to an *n*-Bu ligand from the cuprate.[23] When more forceful conditions of excess cuprate with heating were employed, the reaction was driven further toward completion (entry 3), with moderate yields of **10** and formation of **13**. Reactions with the ethyl nucleophile also manifested that

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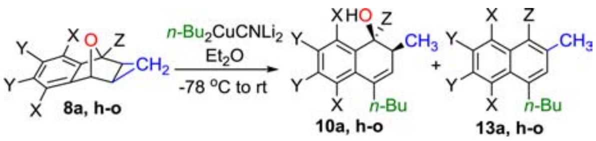
the longer the reaction was left, the greater the consumption of starting material and formation of side product **13** (entries 4–6). A similar observation was made for the hexyl nucleophile (entries 7 and 8). It soon became evident that aromatization proceeded readily in the sealed reaction vessel under reaction conditions. Upon closer examination, it also became apparent that **10** converts to **13** on standing at room temperature over time.[24] Finally, *i*-Pr and *t*-Bu nucleophiles showed relatively fast conversion, although similar proportions of **10** and **13** were recovered (entries 9 and 10), while surprisingly, the phenyl nucleophile appeared to produce **10** without any recoverable **13** (entry 11).

The scope of the ring-opening reactions of derivatized cyclopropanes **8**, bearing various substituents on the arene as well as at the bridgehead position, is summarized in Table 3.

Table 3. Effects of Substitution Pattern on the Substrate toward Type 1 Ring-Opening Reactions



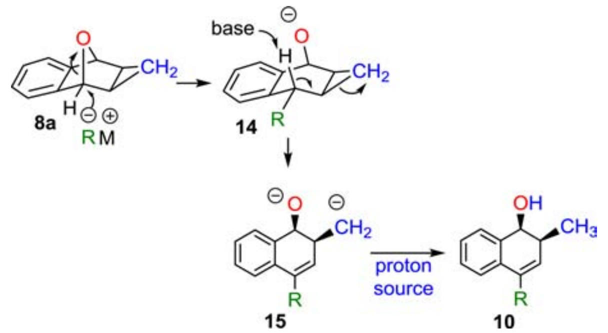
entry	X	Y	Z	time (h)	8 (%)[a]	(%)[a] 10	13
1	H	H	H	8	2	95	2
2	Me	H	H	4	9	64	0
3	OMe	H	H	1	78	15	7
4	OMe	H	H	20	53	24	14
5	OMe	H	H	48	31	12	51
6	H	OMe	H	160	96	0	0
7	H	H	Me	48	35	59	4
8	H	H	Me	120	9	48	21
9[b]	H	H	Et	140	7	81	12
10	H	H	*n*-Bu	160	20	76	0
11	H	H	*t*-Bu	160	22	61	0
12[c]	H	H	Br	15	5	93	0

[a]Isolated yield after column chromatography. [b]5 equiv of organocuprate. [c]Z = H in **10**.

Relative to the unsubstituted reaction of **8a** (entry 1), substrates bearing *para*-disubstituted arenes appeared to show moderate reactivity toward ring-opening with surprisingly short duration (entries 2 and 3). Once again, it was observed that reactions left for longer periods experienced extensive aromatization (entries 3–5). In contrast, the *ortho*-dimethoxy derivative showed no signs of reacting (entry 6), which was not surprising as we have previously observed similar differences in reactivity between these *ortho*- and *para*-compounds in our laboratories.[25] C1-Alkyl-substituted substrates all showed good reactivity and high regioselectivity but required longer reaction times overall (entries 7–11). C1-Methyl-substituted **8** showed moderate conversion after 48 h, although it was not until the reaction was left for nearly a week that the consumption of **8** was near completion (entries 7 and 8). Ethyl and *n*-butyl substituents gave >75% yields of **10** with minimal or undetectable **13** after 140–160 h (entries 9 and 10). The ring-opening also worked for the bulky C1-*t*-Bu substituent, which gave no **13** (entry 11). Finally, when a C1-bromo-substituted substrate was subjected to the ring-opening reaction, the product did not contain the halogen, but instead had a hydrogen in its place.[26] Moreover, the reaction gave comparable yields of 93% to that of the unsubstituted parent substrate **8a** (entry 12).

To account for the formation of **10** in Type 1 ring-opening reactions, we propose a general mechanism (Scheme 4).

Scheme 4. Proposed Mechanism for Type 1 Ring Openings



Following attack of an organometallic nucleophile at the bridgehead position of **8a** and cleavage of its C–O bond to give **14**, a basic species present in the reaction medium removes a bridgehead proton. This causes an internal rearrangement of electrons in the framework which forces open the cyclopropane, generating **15**. Upon quenching, both anionic C and O atoms of **15** would become protonated, giving rise to the observed product, **10**.

In summary, we have demonstrated the first examples of Type 1 organocopper-mediated ring-opening reactions of cyclopropanated 7-oxabenzonorbornadienes as a novel approach for the preparation of 2-methyl-1,2-dihydronaphthalen-1-ols. This chemistry is applicable to the incorporation of primary, secondary, tertiary and aromatic organic nucleophiles as well as to substrates bearing *para*-arene substituents and C1-bridgehead substituents. In addition, complete regioselectivity was observed for reactions involving C1-substituted substrates. Further investigations including mechanistic studies and broadening of the reaction scope will continue in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization 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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(24) The conversion to **13** was monitored by ^{1}H NMR in $CDCl_3$ over a period of 2 months. See the Supporting Information.
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(26) The product **10o** where Z = H was identified by comparison of its ^{1}H and ^{13}C NMR spectra to that of **10a** formed by reacting **8a** with *n*-Bu nucleophile. See the Supporting Information.

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