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Ni-Catalyzed β-Alkylation of Cyclopropanol-Derived Homoenolates

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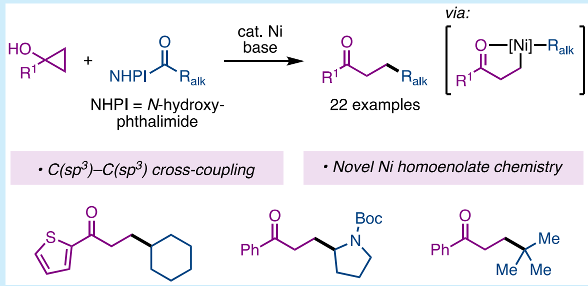
Supporting Information

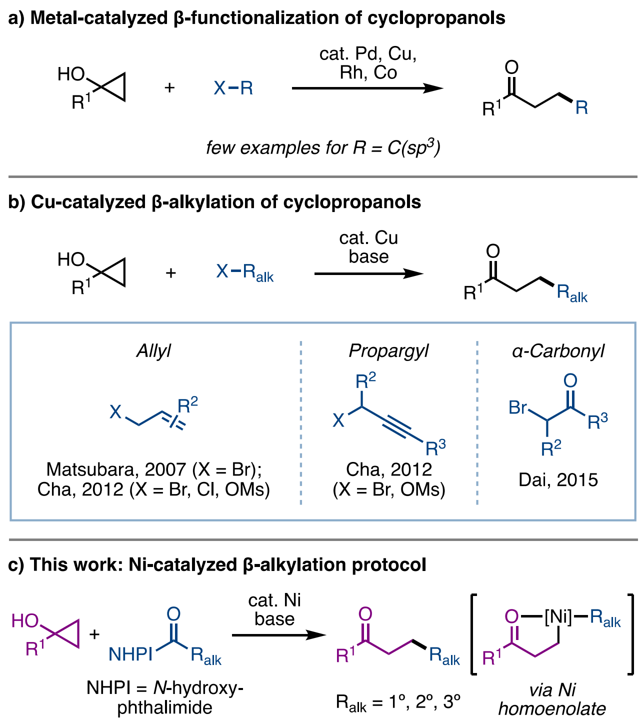
ABSTRACT: Metal homoenolates are valuable synthetic intermediates which provide access to β-functionalized ketones. In this report, we disclose a Ni-catalyzed β-alkylation reaction of cyclopropanol-derived homoenolates using redox-active *N*-hydroxyphthalimide (NHPI) esters as the alkylating reagents. The reaction is compatible with 1°, 2°, and 3° NHPI esters. Mechanistic studies imply radical activation of the NHPI ester and 2e β-carbon elimination occurring on the cyclopropanol.



The chemistry of metal homoenolates has a rich history,[1] and recent years have seen a resurgence of transition-metal-catalyzed transformations of homoenolates.[2,3] The metal homoenolate is an interesting synthetic intermediate since it exhibits umpolung reactivity that can be exploited for facile, selective β-functionalization of carbonyl derivatives with electrophiles. Cyclopropanols are ideal metal homoenolate precursors since they are bench stable and can be readily accessed in a few steps from inexpensive starting materials.[2,4] A number of methods have now been reported for the coupling of various functional groups with cyclopropanol-derived homoenolates.[2−4] For β-carbon−carbon bond-forming reactions, the most versatile metals are Pd, Cu, Rh, and Co, and arylation, alkenylation, alkynylation, and allenylation methods using these metals have been reported (Scheme 1a).[2,3,5] Notably, the most common of these transition-metal-catalyzed protocols are those entailing the installation of $C(sp^2)$ or $C(sp)$ functional groups, and protocols which achieve β-alkylation of cyclopropanol-derived homoenolates are limited.

It is recognized that nonplanar motifs are desirable in drug discovery, and there is a desire for the synthesis of $C(sp^3)$-rich molecules which can help "escape the flatland".[6] In this vein, the C-alkylation of cyclopropanol-derived homoenolates represents an interesting strategy for the synthesis of β-alkyl ketones. While selected examples of β-alkylation of cyclopropanol-derived homoenolates have been reported, these protocols are currently only applicable to specific substrate classes (Scheme 1b). Matsubara and co-workers reported the Cu-catalyzed allylation of Zn cyclopropoxides,[7] and in 2012, Cha and co-workers reported a similar strategy for the allylation and propargylation of cyclopropanols.[8] In 2015, Dai and co-workers showed that α-bromocarbonyls are also viable alkylating reagents under Cu catalysis.[9] While these protocols are convenient, they are restricted to specific substrate classes, and to date, a strategy for β-alkylation of

Scheme 1. β-Functionalization and β-Alkylation of Cyclopropanol-Derived Homoenolates



cyclopropanols with a broad range of alkyl electrophiles has not been reported.[10−12]

Inspired by recent work on Ni-catalyzed reactions of redox-active *N*-hydroxyphthalimide (NHPI) esters reported by the groups of Baran[13] and Weix,[14] we wondered if NHPI esters

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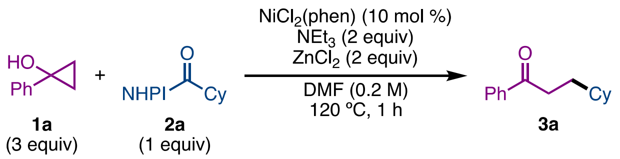
Org. Lett. XXXX, XXX, XXX−XXX

could be used for the β-alkylation of cyclopropanol-derived Ni homoenolates. This $C(sp^3)-C(sp^3)$ cross-coupling would be inherently challenging due to the propensity of the $C(sp^3)$ coupling partners to undergo β-hydride elimination and protodemetalation.[15] As alkylating reagents, NHPI esters are advantageous since they are readily prepared from abundant carboxylic acids, are easy to handle, and possess low toxicity in comparison to their alkyl halide counterparts.[16]

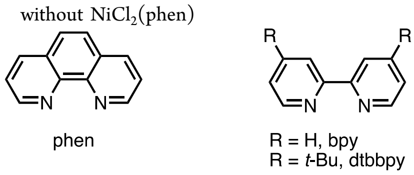
Herein, we report a Ni-catalyzed β-alkylation of cyclopropanol-derived homoenolates using NHPI esters (Scheme 1c). This methodology is viable for 1°, 2°, and 3° NHPI esters, tolerates a number of functional groups, and can be applied to the late-stage functionalization of medicinally relevant substrates. There are limited reports on the chemistry of Ni homoenolates,[17] and this procedure represents one of the first instances of a reaction employing cyclopropanol-derived Ni homoenolates.[3]

The optimal conditions for the β-alkylation of cyclopropanol-derived homoenolates are shown in Table 1. Using

Table 1. Optimization of the Reaction[a]



entry	deviation from std cond	yield of 3a[b] (%)
1	none	85[c]
2	using $NiCl_2$(bpy) (10 mol %)	81
3	using $NiCl_2$(dtbbpy) (10 mol %)	54
4	without NEt_3	3
5[d]	NaH (3 equiv) instead of NEt_3	0
6[d]	Et_2Zn (1.5 equiv) instead of NEt_3	20
7	$MgCl_2$ instead of $ZnCl_2$	12
8	without $ZnCl_2$	40
9	without $NiCl_2$(phen)	0



[a]Reaction conditions: cyclopropanol **1a** (40 mg, 0.30 mmol), ester **2a** (27 mg, 0.10 mmol), $NiCl_2$(phen) (3.1 mg, 0.010 mmol), $ZnCl_2$ (27 mg, 0.20 mmol), NEt_3 (28 μL, 0.20 mmol), DMF (0.50 mL), 120 °C, 1 h. [b]GC−MS yields based on *n*-dodecane as internal standard. [c]Average of three runs. [d]Base was prestirred with cyclopropanol **1a** for 5 min at rt in DMF before combining with the other reaction components. dtbbpy = 4,4′-di-*tert*-butyl-2,2′-dipyridyl; NHPI = *N*-hydroxyphthalimide; phen = 1,10-phenanthroline.

1-phenylcyclopropanol (**1a**) and redox-active *N*-hydroxyphthalimide ester **2a** as model substrates, the desired β-alkylketone product **3a** could be formed in 85% yield in the presence of $NiCl_2$(phen) (10 mol %), triethylamine (2 equiv), and $ZnCl_2$ (2 equiv) in DMF at 120 °C after 1 h. While $NiCl_2$(phen) was determined to be the most optimal and general precatalyst, a number of other precatalyst/ligand combinations delivered **3a** in practical yields (e.g., $NiCl_2$(bpy) or $NiCl_2$(dtbbpy), entries 2 and 3; see also Table S2). Triethylamine (2 equiv) was vital for the success of the reaction; performing the reaction without triethylamine gave only 3% yield of **3a** (entry 4). Other weak bases were less competent (Table S1). Pretreating **1a** with a strong base like NaH (3 equiv) or Et_2Zn (1.5 equiv) to generate the cyclopropoxide salt in situ resulted in very low yields of **3a** (entries 5 and 6), suggesting that preformation of a metal cyclopropoxide or metal homoenolate is not productive for this reaction. For these reactions, a significant side product was the ester resulting from transesterification of **2a** with **1a**.[18] Though some product was formed in the absence of $ZnCl_2$ (40%, entry 8), $ZnCl_2$ was ultimately necessary for optimal yields, and the use of other Lewis acids ($MgCl_2$, entry 7; see also Table S1) did not give comparable yields. The role of $ZnCl_2$ is currently unclear, though we believe it may act as a Lewis acid to help activate **2** and stabilize the radical anion intermediate generated after reduction of **2**.[19] Finally, performing the reaction in the absence of a Ni catalyst (entry 9) resulted in no detectable yield of **3a**.

A particular challenge in the development of this reaction is the propensity of **1a** to undergo rapid ring-opening isomerization to the ketone (i.e., propiophenone),[20] which occurs at temperatures as low as rt and which is mediated efficiently by $ZnCl_2$ at 120 °C (see Table S7 for details). The rapid isomerization of **1a** under the reaction conditions is the primary reason for requiring an excess of **1a**. This isomerization represents a formal migration of the alcohol proton on **1a**; however, strategies for eliminating the proton, such as stoichiometric deprotonation (entries 5 and 6), or using a TMS-protected cyclopropanol (Table S4),[21] were not successful. Preliminary kinetic analysis is consistent with isomerization of **1a** on the time scale of formation of **3a**, suggesting that these pathways are competitive. Thus, one reason for this reaction's high temperature may be to promote productive intermolecular coupling (see Table S3 for temperature data). It is also worth noting that the reaction of **1a** and **2a** under standard conditions is complete within 5 min.[22] For the same reaction using 1-benzylcyclopropanol instead of **1a**, the reaction is complete within 30 min.

A summary of β-functionalized ketones that have been prepared using this protocol is shown in Table 2. The reaction is tolerant of 1-arylcyclopropanols with various substituents, including electron-rich (**3b**, **3c**, **3j**, **3k**, **3l**) and electron-neutral (**3d**) substituents as well as a 1-heteroarylcyclopropanol (**3f**). 1-Alkyl-substituted cyclopropanols are competent substrates as well (**3g**, **3h**, **3i**, **3s**), though they react more efficiently in DMA than DMF (see Table S4). Cyclopropanol derivatives with substituents at C2 and C3 were generally not competent under the current conditions (Table S6). In terms of compatible NHPI esters, 2° esters with various steric properties (**3a**, **3k**, **3l**) are compatible coupling partners, as are 1° alkyl esters (**3j**, **3r−3u**), 1° benzylic esters (**3v**), and 3° esters (**3n**). The α-amino NHPI ester derived from *N*-Boc proline (**3d−3e**, **3h−3i**, **3m**) was also compatible; the corresponding alkyl halide coupling partner would be challenging to prepare and handle, clearly highlighting an advantage of using NHPI esters in this cross-coupling protocol. The reaction is tolerant of various functional groups including carbamate (**3m**, **3p**), urea (**3o**), amide (**3q**), ester and alkene (**3u**), and aryl chloride (**3v**). The use of complex substrates **3j**, **3t−3v** demonstrates how this protocol might be applicable to late-stage β-alkylation in the context of complex target synthesis.[23] For some substrates, it was also found that $NiCl_2$(dtbbpy) outperformed $NiCl_2$(phen); it appears that $NiCl_2$(dtbbpy) may be the more suitable catalyst for reactions of 1° NHPI esters (**3r**) or for substrates bearing Lewis basic

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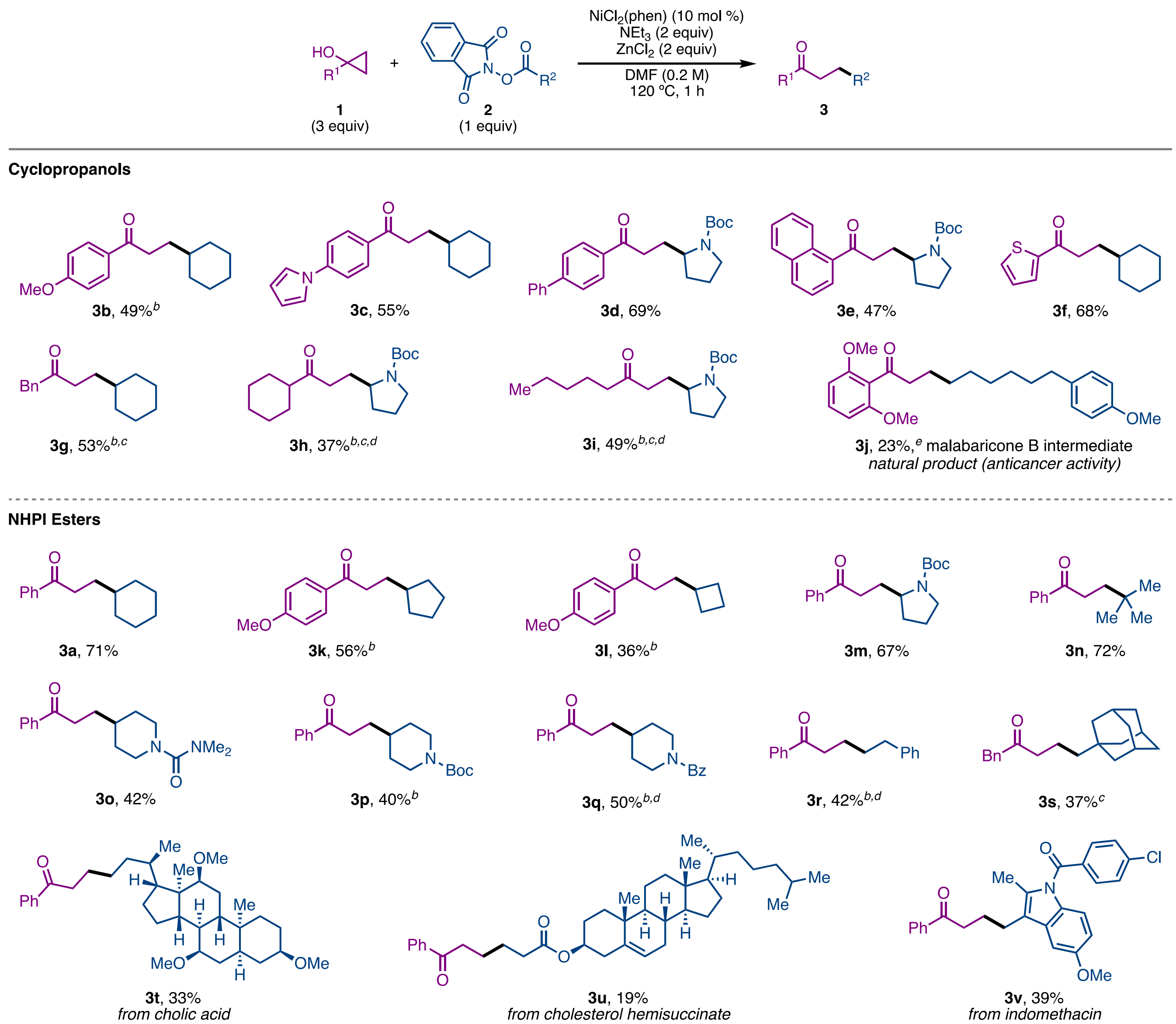
Org. Lett. XXXX, XXX, XXX−XXX

Table 2. Scope of the reaction[a]



[a]Reactions performed on 0.20−0.30 mmol scale. Yields are for isolated material; [b]Performed in duplicate; displayed yield is the average of two runs. [c]Using DMA (0.20 M) instead of DMF. [d]Using $NiCl_2$(dtbbpy) (10 mol %); see the Supporting Information for yields using $NiCl_2$(phen); [e]Performed on 0.10 mmol scale. dtbbpy = 4,4′-di-*tert*-butyl-2,2′-dipyridyl; NHPI = *N*-hydroxyphthalimide. For supplementary examples see SI (Table S5).

functional groups (**3i**, **3q**) (see the Supporting Information for details).

Experiments that were performed to better understand the reaction mechanism are shown in Scheme 2. When enantiopure NHPI ester **2b** was exposed to the reaction conditions, complete loss of stereochemical information was observed (Scheme 2a). Also, when alkene-containing substrate **4** was employed in a standard reaction with **1a**, 35% of the 5-*exo-trig*-cyclized product **5** was observed (Scheme 2b), with >20:1 selectivity for **5** over the corresponding uncyclized alkene. These results are consistent with the generation of radical intermediates from the NHPI ester starting material. Next, bicyclic cyclopropanol **1b** was exposed to the reaction conditions. Bicyclic cyclopropanol derivatives are known to undergo exocyclic ring-opening under polar (two-electron) mechanisms[2] and endocyclic ring-opening via radical (one-electron) mechanisms.[24,25] When bicyclic cyclopropanol **1b** was treated with **2a** under standard conditions, product **3w** was isolated in 13% yield. Product **3w** was the only detectable *β*-alkylketone isomer by GC−MS, which is consistent with a two-electron *β*-carbon elimination pathway. The remaining mass balance of **1b** in this reaction went to the ring-opened isomer.

A likely mechanism for this transformation is shown in Scheme 3. Starting with the Ni(II) precatalyst, catalyst activation may occur via disproportionation to generate Ni(I)−X species **6**.[26] From **6**, ligand exchange with **1** and deprotonation by Et_3N can form Ni(I) cyclopropoxide **7**. Cyclopropoxide **7** is in equilibrium with Ni(I) homoenolate **8**, though it is presently unknown to which side this equilibrium lies.[27,28] Then single-electron transfer (SET) to NHPI ester **2**, followed by fragmentation and recombination, generates Ni(III) homoenolate **9**. Finally, reductive elimination releases

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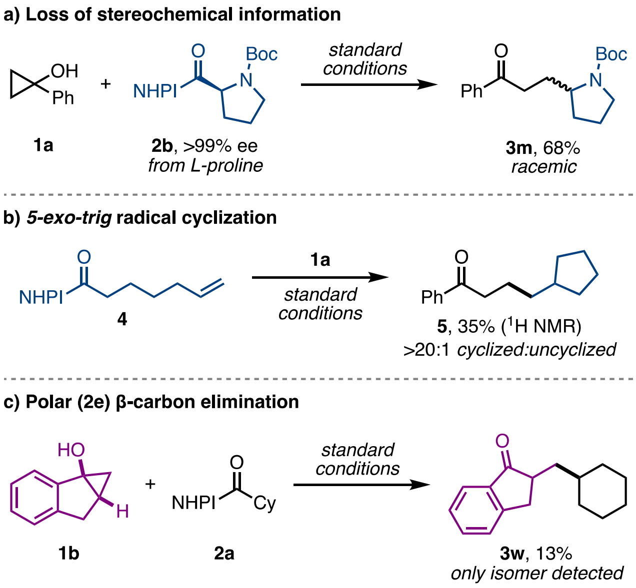
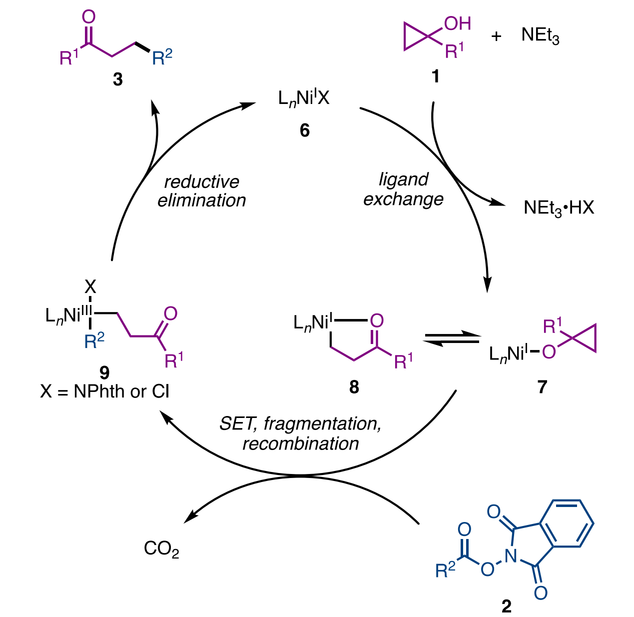
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Mechanistic Experiments[a]



[a]See the Supporting Information for full experimental details.

Scheme 3. Proposed Catalytic Cycle



desired product **3** and regenerates Ni(I) species **6**. It is possible that $ZnCl_2$ helps form cyclopropoxide or homoenolate intermediates from **1**, which could be beneficial for the ligand exchange (or transmetalation) steps.[8] However, since the reaction also proceeds in the absence of $ZnCl_2$ (Table 1, entry 8), and since a preformed Zn homoenolate is not a competent intermediate (Table 1, entries 5 and 6), we believe homoenolate formation occurs predominantly on the Ni center.

In conclusion, we have developed a Ni-catalyzed protocol for the β-alkylation of cyclopropanol-derived homoenolates using redox-active NHPI esters. Using this method, a variety of β-alkyl ketones can be prepared. There is a very limited number of reports on the chemistry of Ni homoenolates, and we anticipate many interesting opportunities for reaction development exploiting these intermediates.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03435.

Reaction optimization tables, mechanistic studies, synthetic procedures, and characterization data (PDF)

NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(28) The "transmetalation-first" pathway proposed here is informed by typical reaction mechanisms for Ni(I)/Ni(III) catalytic cycles, though it is also possible that ligand exchange occurs after oxidative addition. We favor the pathway proposed for two empirical reasons: (1) side products arising from side reactions of the NHPI ester (reduced and homocoupled dimer side products) have been virtually undetected in this reaction, suggesting that **2** is consumed at a stage in the catalytic cycle where product formation is possible and facile; (2) unproductive protodemetalation from a homoenolate intermediate such as **8** seems likely in the case where the Ni catalyst has interacted with **1** but not **2**, i.e., where product formation is not facile, and this unproductive pathway can explain the major ring-opened side product in this reaction.

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