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

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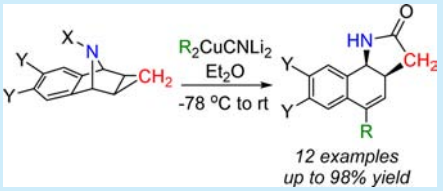
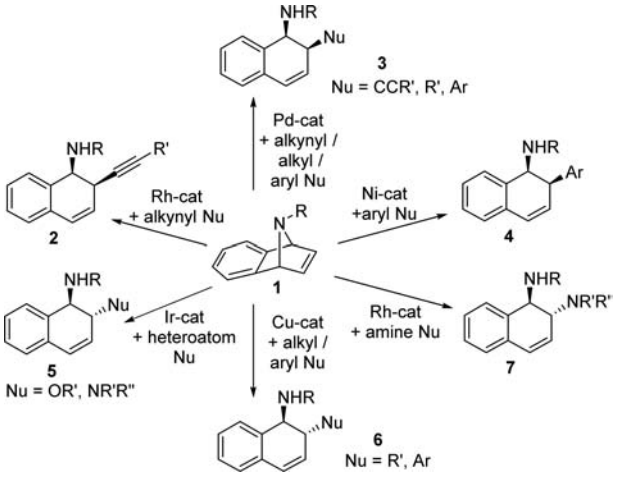
Supporting Information

ABSTRACT: The first nucleophilic ring-opening reactions of cyclopropanated 7-azabenzonorbornadienes have been achieved using organocuprates. Tricyclic or tetracyclic γ-lactams were obtained as the sole product in good yields of up to 98% when alkoxycarbonyl groups occupied the N-substituent position. Successful conversions to lactams were observed for primary, secondary, tertiary, and aromatic nucleophiles, as well as for a variety of substrates functionalized on the benzene ring. A possible mechanism for these transformations is discussed.



Ring-opening reactions of azabicyloalkenes have allowed for efficient syntheses of highly substituted structures such as alkaloid natural products,[1] analgesics,[2] and chiral ligands.[3] In the past decade alone, research in nucleophilic ring-opening reactions of 7-azabenzonorbornadienes **1** has seen an especially rapid growth (Scheme 1).

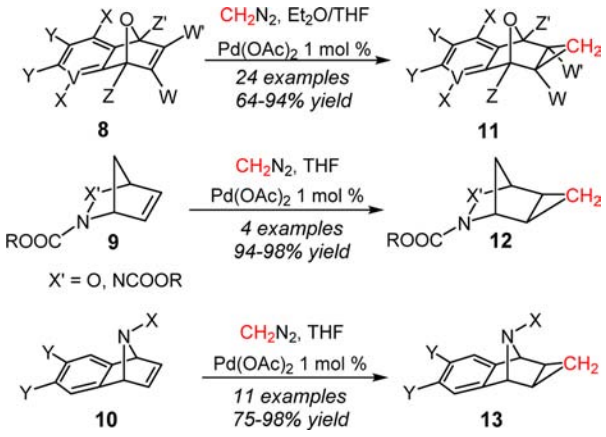
Scheme 1. Transition-Metal Catalyzed Nucleophilic Ring-Opening Reactions of 7-Azabenzonorbornadienes



As with reactions of other heterobenzonorbornadienes,[4] the combination of transition metal catalyst and nucleophile dictates the stereochemical outcome of ring-opening reaction of **1**, and these transformations have been shown to tolerate a wide variety of functional groups. For instance, rhodium-catalyzed openings using alkynyl nucleophiles,[5] palladium-catalyzed openings with alkynyl,[6] alkyl,[7] or aryl nucleophiles,[8] and nickel-catalyzed openings with aryl nucleophiles[9] all produce *cis* stereochemical products **2**–**4**. In contrast, iridium-mediated openings with carboxylic acid,[10] alcohol,[11] or amine nucleophiles,[12] copper-catalyzed reactions with alkyl and aryl nucleophiles,[13] and rhodium-catalyzed reactions with amine nucleophiles[14] result in *trans* stereochemical products **5**–**7**.

While reactions of heterobicycloalkenes such as **1** have become widespread, little is known regarding the use of their cyclopropanated versions as synthons. Cyclopropanes are thought to behave much like alkenes,[15] with an additional carbon that could serve as a handle for further derivatization. We have recently developed a stereoselective cyclopropanation of [2.2.1] heterobicycloalkenes **8**–**10** under palladium-mediated conditions, obtaining *exo* cyclopropanated products **11**–**13** in appreciable yields (Scheme 2).[16] Using these, we have investigated the ring-opening of cyclopropanated 7-oxabenzonorbornadienes **11** and found that by employing organocuprates as nucleophiles, a large collection of 1,2-*cis*-dihydronaphthalen-1-ols **14** could be prepared in moderate to excellent yields (Scheme 3).[17] In this early report we also proposed a mechanism for the

Scheme 2. Recent Preparations of Cyclopropanated [2.2.1] Heterobicycloalkenes[16]



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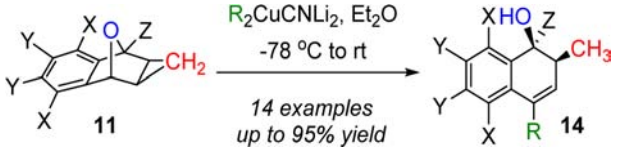
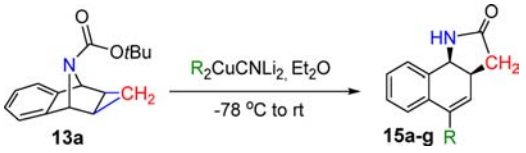
Scheme 3. Ring-Opening Reactions of Cyclopropanated 7-Oxabenzonorbornadienes with Cyanocuprates[17]



formation of the dihydronaphthalenol products **14**. To gain further insight on this mechanism and to better gauge the scope of reactivity of cyclopropanated heterobicycloalkenes, we next decided to investigate the structurally analogous cyclopropanated 7-azabenzonorbornadienes **13** under similar reaction conditions[17] of organocuprate-mediated nucleophilic ring-opening.

Much to our surprise, when the optimized reaction conditions using higher-order cyanocuprate were applied to substrate **13a**, the expected product containing an *N*-COO*t*Bu functionality did not arise, but instead γ-lactam **15a** was observed (Table 1, entry 1). Although this reaction was incomplete at 7 h, after a full day it was found to go to completion with no starting material recoverable (entry 2). In comparison to cyclopropanated oxabenzonorbornadiene **11**, which underwent full consumption after 8 h in our former study,[17] the longer reaction time required for cyclopropanated azabenzonorbornadiene **13** is consistent with the general tendency of azabicyclic compounds having a lower reactivity toward nucleophilic ring-opening reactions than their oxabicyclic counterparts.[10,12c] Various other alkyl or aryl cuprate nucleophiles also produced the corresponding lactams, **15b–g** (entries 3–12). Whereas ethyl (entry 3) and *n*-hexyl (entry 4) nucleophiles showed comparable reactivity to that of *n*-butyl (entries 1–2), the methyl nucleophile was particularly inert, resulting in 89% recovery of **13a** after almost 6 days at room temperature (entry 5). A similar reluctance of methyl nucleophile to react was seen in our previous study with oxygen analogue **11**[16] and can be explained by the low transferability of methyl relative to *n*-Bu ligand from the cuprate.[18] Upon use of excess cuprate with heating, the starting material was fully consumed although the product appeared to have decomposed through prolonged heating and could not be isolated (entry 6). Instead, use of excess cuprate at room temperature resulted in 75% yield of the desired product after 1 day (entry 7). Reaction with *iso*-propyl nucleophile preceded smoothly furnishing 73% product in 24 h (entry 8), whereas *tert*-butyl nucleophile proved to be less reactive and required a longer reaction time of 96 h to reach completion (entries 9–11). This again may involve factors besides steric effects, as the phenyl nucleophile was able to react efficiently in 24 h (entry 12).

Table 1. Effects of Various Organocuprate Nucleophiles on Type 1 Ring-Opening Reactions of 13a

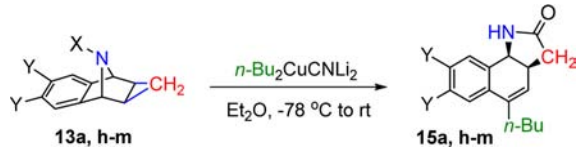


entry	nucleophile	time (h)	recovered **13a** (%)[a]	yield **15** (%)[a]
1	*n*Bu	7	39	58
2	*n*Bu	24	0	92
3	Et	24	0	90
4	Hex	24	0	87
5	Me	140	89	0
6[b]	Me	64	0	0
7[c]	Me	24	0	75
8	*i*Pr	24	0	73
9	*t*Bu	24	73	12
10	*t*Bu	72	31	50
11	*t*Bu	96	0	69
12	Ph	24	0	62

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

Following this, the scope of the ring-opening reactions of functionalized **13**, bearing various substituents on benzene as well as on nitrogen, was examined (Table 2). Relative to the reaction of **13a** (entry 1), substrates with *ortho*-disubstitution on benzene (**13h–j**) showed a range of both lower and higher yields, and no clear distinction of substituent effects could be made from these trials (entries 2–4). When a substrate bearing an *N*-phenyl substituent (**13k**) was subjected to the reaction conditions, no reaction was observed after 1 week (entry 5). Although it is possible that ring-opening may occur for other *N*-aryl compounds bearing strong electron-withdrawing groups, further work is necessary to verify such effects. At the present, it appears that the presence of an *N*-alkoxycarbonyl group is important in activating and promoting the ring-opening transformation at hand. Based on a possible mechanism that could explain the formation of **15** (*vide infra*), it seemed that any *N*-alkoxycarbonyl substrate should produce an identical structure **15a** since the −OR functionality of the carbamate is lost during transformation. To test this, we subjected substrates **13l** and **13m**, respectively bearing *N*-COOMe and *N*-COOBz carbamate functionalities, to the reaction conditions. As expected, the products obtained from **13l** and **13m** were identical to that prepared from **13a**, as confirmed by comparison of their ^{1}H and ^{13}C NMR spectra.[19] Finally, unlike the ring-opening reactions of oxygen analogues **11**, which often underwent aromatization to reduce reaction yields,[17] no aromatization was observed in any of the present trials, allowing for good overall yields of **15** to be obtained (56–98%). The lack of aromatization by dehydration may relate to the poorer nucleofugacity of nitrogen functional groups relative to hydroxyl groups, which easily undergo elimination with a *trans*-hydrogen.[20]

Table 2. Effects of Substrate Functionalities on Type 1 Ring-Opening Reactions of 13



entry	X	Y	time (h)	recovered **13** (%)[a]	yield **15** (%)[a]
1	COO*t*Bu	H	24	0	92
2	COO*t*Bu	Me	24	0	87
3	COO*t*Bu	OMe	24	0	56
4	COO*t*Bu	−(CH=CH)−	24	0	98
5	Ph	H	168	88	0
6	COOMe	H	24	0	87
7	COOBz	H	24	0	86

[a]Isolated yield after column chromatography.

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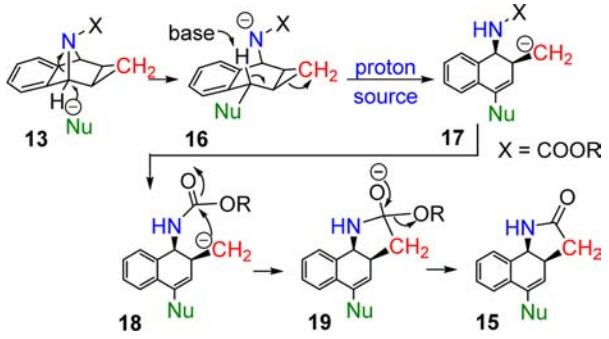
Formation of γ-lactam **15** is thought to take place through a mechanism similar to that of our previously described Type 1 ring-opening reactions of cyclopropanated oxabenzonorbornadienes **11**,[17] where the difference with the azabicyclic version **13** arises when the N-substituent is an electrophilic carbonyl moiety (X = COOR), which allows for an additional nucleophilic acyl substitution to ensue (Scheme 4). Initial attack of organocuprate

Scheme 4. Proposed Mechanism for Type 1 Ring-Opening Reactions of Cyclopropanated 7-Azabenzonorbornadienes



nucleophile at the bridgehead position of **13** causes C−N bond cleavage, generating intermediate **16**. A bridgehead proton is then removed by a basic species in the reaction medium. While the entity of this base is yet to be determined, experiments involving deuterium labeling at the bridgehead position may help identify this species in future works. The deprotonation in **16** promotes an intramolecular reordering of electrons, which cleaves the cyclopropane to form carbanion **17**, while protonation of nitrogen at this stage allows for subsequent attack of its carbanion on the carbamate group of **18**.[21−23] This displaces the alkoxy moiety (**19**) and gives rise to the observed product, **15**.

It is conceivable that if substrates bearing electron-withdrawing groups on the cyclopropane (in place of CH_2) were subjected to the above reaction conditions, another mode of ring-opening may take place instead. For a more complete picture of such reactivities, future ring-opening studies involving cyclopropanated 7-azabenzonorbornadienes should consider substitution on the cyclopropane, as well.

Recently, several literature reports have proposed the importance of core framework **20** (Figure 1).[24,25] Moore and

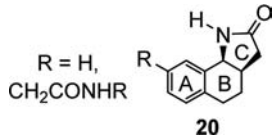


Figure 1. Core framework of carboxylic acid receptor and triazolium precursor.

co-workers describe the design of a heterocyclic receptor for carboxylic acids with geometric confinement to three binding sites, which can be achieved by a five- or six-membered lactam with *cis*-fusion between rings B and C, and a saturated inner ring B.[24] The same *cis*-framework **20** also serves as a precursor to triazolium salts, which can be used to generate chiral carbene catalysts for highly efficient conjugate nucleophilic acylation, transesterification, polymerization, and benzoin condensation reactions.[25] This versatile intermediate may be readily accessible by alkene reduction of lactams **15** of the present work, which would be a likely improvement to the current syntheses of **20**,[24−27] which at best is obtained in 22% over six steps.[24] In addition, further carbonyl reduction of **20** may allow for the preparation of carbocyclic analogues of martinelline receptor antagonists, whose total synthesis has been extensively studied over the years.[28−30]

In summary, through our studies of organocuprate-mediated ring-openings of cyclopropanated 7-azabenzonorbornadiene, we have discovered a novel one-pot synthesis of tricyclic and tetracyclic γ-lactams with 1,2-*cis* stereochemistry. The reaction provides good to excellent yields of lactams containing primary, secondary, tertiary, and aromatic nucleophiles and is applicable to substrates bearing various *ortho*-arene substituents. Formation of γ-lactam provides mechanistic support to our former observation of Type 1 ring-openings with cyclopropanated 7-oxabenzonorbornadienes, and the products obtained in this work may serve as intermediates to the synthesis of heterocyclic receptors and receptor agonists, as well as chiral catalysts.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00757.

Experimental procedures and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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