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Sequential Nucleophilic Arylation/Ring-Contractive Rearrangement of *N*-Alkoxylactams

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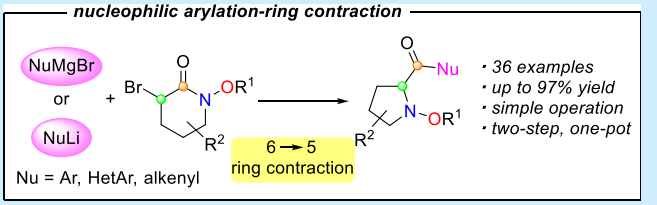
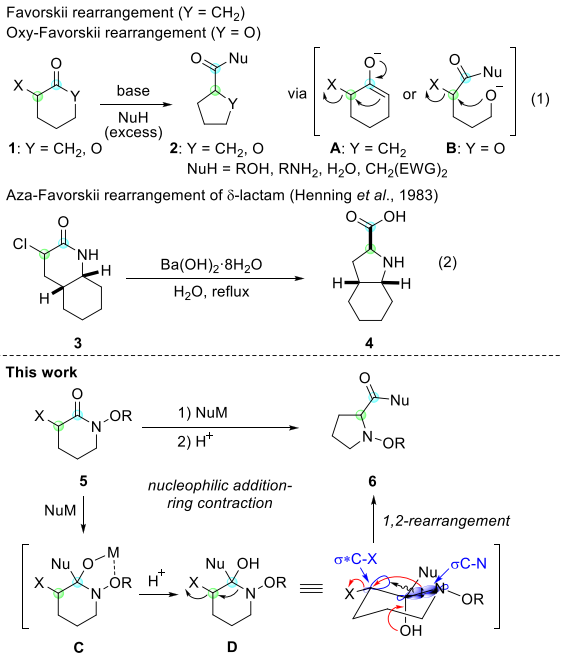
ABSTRACT: A nucleophilic addition/ring-contractive rearrangement of α-bromo *N*-alkoxylactams with organometallic reagents was developed, providing an efficient access to α-acylpyrrolidines incorporating various C(sp^2) units such as aryl, heteroaryl, and alkenyl groups. The sequential reaction proceeds through a five-membered chelate formation using nucleophilic addition followed by ring contraction via the formation of *N,O*-hemiaminal with good yields and a broad substrate scope. Moreover, a preliminary result with the use of the chiral *N*-alkoxylactam for the diastereoselective reaction is described.



In synthetic organic chemistry, the ring-contraction reaction is one of the most elegant transformations because it allows the skeletal reorganization with a high level of selectivity in several cases, affording products not easily accessible by other approaches.[1] In particular, the ring-contraction reaction involving the migration of carbonyl group is an attractive and useful reaction due to the further introduction of a nucleophile to the migrated carbonyl group. This reaction proceeds via the rearrangement of several C−C bonds, and representative examples include the pinacol rearrangement,[2] Wolff rearrangement,[3] Favorskii rearrangement,[4] and benzylic acid rearrangement.[5] Therefore, these ring contraction strategies are applied for the synthesis of biologically active and natural products.[6] The Favorskii rearrangement is a base-induced ring contraction of α-halo cyclic ketones (**1**: Y = CH_2) that enables the migration of the endocyclic carbonyl group as well as the incorporation of *N*- and *O*-nucleophiles (ROH, R_2NH, RNH_2) to afford ring-contracted carboxylic acid derivatives (**1** → **A** → **2**: Y = CH_2) (Scheme 1, eq 1).[7] In contrast, the Favorskii rearrangement accompanied by introduction of *C*-nucleophiles has received little attention.[8] Moreover, available *C*-nucleophiles are limited to stabilized enolates. The reaction utilizing lactones and lactams would construct ring-contracted cyclic ethers and amines. For example, the oxy-Favorskii rearrangement of α-halo lactones (**1**: Y = O) proceeds through the ring-opening and intramolecular S_N2-type cyclization of alkoxide intermediate **B** to provide α-acylated cyclic ethers (**2**: Y = O).[9] However, the aza-Favorskii rearrangement of α-halo lactams is scarce.[10] Therefore, systematic studies were not conducted due to the poor electrophilicity of the amide carbonyl group. For example, Henning and co-worker reported that the ring-contraction reaction of α-chloro lactam **3** followed by the introduction of an *O*-nucleophile under basic conditions afforded the α-carboxylated pyrrolidine derivative **4** (Scheme 1, eq 2).[10a] To

Scheme 1. Representative Examples of the Favorskii and Other Types of Favorskii Rearrangements, Including the Inspiration for This Work



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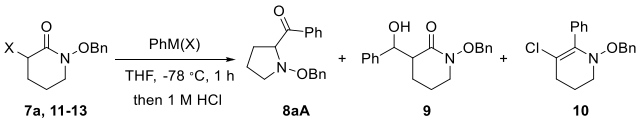
the best of our knowledge, there are no studies on the incorporation of *C*-nucleophiles in the aza-Favorskii rearrangement of α-halo lactams, even though the carbonyl group migrating in the reaction can serve as an effective proxy for a wide variety of other functional groups. Therefore, the C−C bond forming ring contraction of lactam remains a major synthetic challenge.[11] Herein, we present the sequential nucleophilic arylation/ring contraction of δ-lactam for the synthesis of α-acylpyrrolidines.[12]

To introduce a *C*-nucleophile into an amide carbonyl group, using the Weinreb amide is one of the most reliable and powerful methods.[13] The *N*-alkoxy group of a Weinreb amide increases the electrophilicity of the amide carbonyl group and then allows the nucleophilic addition under mild conditions. Therefore, we surmised that the α-halo *N*-alkoxylactam **5** would act as a good acylating agent to introduce *C*-nucleophiles, such as organometallic reagents (Scheme 1, this work). The nucleophilic addition of organometallic reagents to lactam **5** leads to the formation of the five-membered chelated intermediate **C**. The acidic workup of the chelated intermediate **C** results in the generation of the *N*,*O*-hemiaminal **D**, which rapidly undergoes a 1,2-rearrangement through the overlap of an antibonding orbital on the C−X bond (σ^*_{C-X}) and a bonding orbital on the C−N of the hemiaminal group (σ_{C-N}) to obtain α-acylpyrrolidines **6**.[14] The α-bromo *N*-alkoxylactam **5** (X = Br) was used to investigate the possibility of the nucleophilic arylation/ring contraction with an organometallic reagent because the α-bromo group as a leaving group has the requisite reactivity for the ring contraction and would be tolerant in the nucleophilic addition to the amide carbonyl group without halogen−metal exchange.[15]

The nucleophilic addition/ring contraction of α-bromo *N*-benzyloxylactam **7a** as a model substrate was initially investigated (Table 1). The model substrate **7a** was readily

Table 1. Optimization of Nucleophilic Addition/Ring Contraction



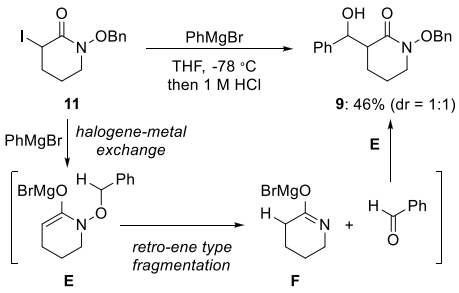
7a, 11-13 **8aA** **9** **10**

entry	substrate	PhM(X) (equiv)	yield (%)
1	**7a** (X = Br)	PhMgBr (1)	**8aA**: 67[b]
2	**7a** (X = Br)	PhMgBr (2)	**8aA**: 97
3	**7a** (X = Br)	PhLi (2)	**8aA**: 71
4	**11** (X = I)	PhMgBr (2)	**8aA**: ND[c], **9**: 46[d]
5	**12** (X = Cl)	PhMgBr (2)	**8aA**: ND[c], **10**: 73
6	**13** (X = OTs)	PhMgBr (2)	**8aA**: 30
7[e]	**7a** (X = Br)	PhMgBr (2)	**8aA**: 97

[a]Yield of the chromatographically pure product. [b]Lactam **7a** was recovered in 25% yield. [c]Not detected. [d]dr = 1:1. [e]Lactam **7a** (1.24 mmol) was used.

prepared by α-bromination of 5-bromovaleryl chloride followed by amidation and cyclization. The nucleophilic phenylation of **7a** was performed with phenylmagnesium bromide (PhMgBr, 1 equiv) in THF at −78 °C and then quenched with 1 M HCl. The phenylation/ring contraction proceeded smoothly to give α-benzoylpyrrolidine **8aA** in good yield along with recovered **7a** (Table 1, entry 1). It should be noted that this is the first example for a nucleophilic phenylation of lactam and sequential ring contraction. Pleasingly, the phenylation/ring contraction of **7a** provided the desired compound **8aA** in excellent yield with 2 equiv of PhMgBr (entry 2). Phenyl lithium (PhLi) was also suitable for this sequential reaction, whereas using other organometallic reagents was not effective (entry 3 and data not shown).[16] The effects of the α-leaving group on the sequential reaction were then examined. The sequential reaction of α-iodo *N*-benzyloxylactam **11** with PhMgBr afforded the α-benzaldehyde adduct **9** via the aldol-type addition of enolate **E** to benzaldehyde, which was generated by retro-ene fragmentation of enolate **E** (entry 4 and Scheme 2).[13i] In contrast, the use of

Scheme 2. Proposed Reaction Pathway of α-Iodo Lactam 11 with PhMgBr

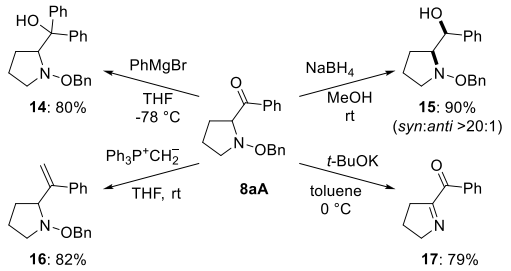


11 **9**: 46% (dr = 1:1)

12 carrying an α-chloro group furnished the chloroenamine **10**, which was produced by nucleophilic phenylation and dehydration (entry 5). The sequential reaction of **13** with the α-tosyloxy group afforded α-benzoylpyrrolidine **8aA**, but in low yield (entry 6). Therefore, the α-bromo group as a leaving group of **7a** plays an important role in the nucleophilic phenylation/ring-contraction reaction. Additionally, it is noted that the reaction could also be carried out in 1 mmol scale without any problem (97% yield, entry 7).

To demonstrate the synthetic utility of the ring-contracted products, α-benzoyl *N*-(benzyloxy)pyrrolidine **8aA** was used to derive various pyrrolidinyl compounds (Scheme 3). The

Scheme 3. Transformations of *N*-Alkoxypyrrolidine 8aA



14: 80% **15**: 90% (*syn*:*anti* >20:1) **16**: 82% **17**: 79%

transformation of **8aA** into pyrrolidinyl alcohols **14** and **15** by the nucleophilic phenylation with PhMgBr and reduction with $NaBH_4$ was successful. The synthesis of pyrrolidinyl alkene **16** was achieved through C−C bond formation using the Wittig reaction. Moreover, the benzyloxy moiety of **8aA** was removed by *t*-BuOK to afford pyrroline **17** via the E1cB reaction.

After the optimal conditions for the nucleophilic addition/ring contraction were established, the reaction of α-bromo *N*-benzyloxylactam **7a** with a variety of aryl Grignard reagents

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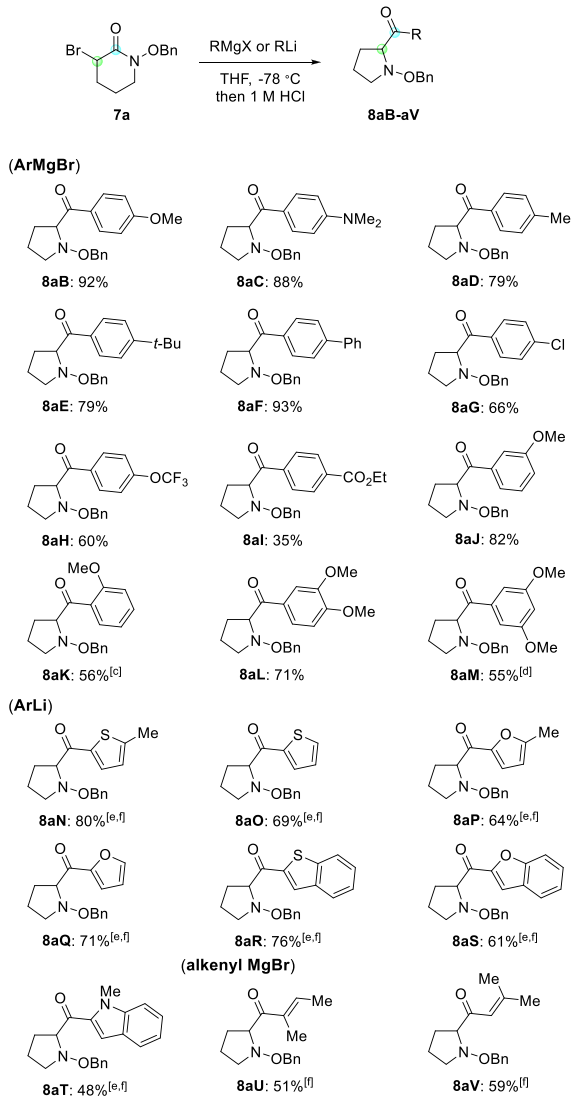
was investigated (Scheme 4). The electronic nature of the substituents on the benzene ring had a moderate effect on the

Scheme 4. Nucleophilic Addition/Ring Contraction of 7a with Various ArMgBr, HetArLi, and Alkenyl MgBr[a,b]



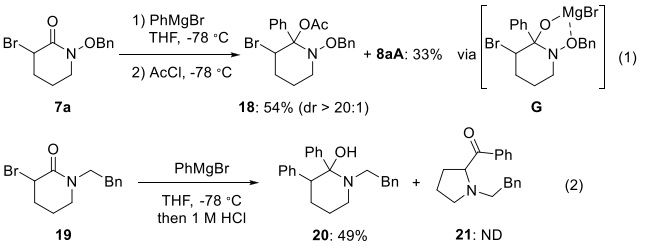
[a]Reaction conditions: **7a** (0.15 mmol), organometallic reagent (0.30 mmol), THF (2 mL), − 78 °C 1−2 h, then 1 M HCl. [b]Yield of the chromatographically pure product. [c]The reaction was carried out at 0 °C. [d]ArMgCl was used. [e]ArLi was *in situ* prepared from ArH and *n*-BuLi (See Supporting Information). [f]The reaction was quenched by AcOH.

reaction efficacy. Higher yields of the desired α-acylpyrrolidines **8aB−aF** were observed, when aryl Grignard reagents with an electron-donating group on the benzene ring, such as the *p*-methoxy, *p*-dimethylamino, *p*-methyl, *p*-*tert*-butyl, and *p*-phenyl group, were used. Moreover, the sequential reaction of **7a** with aryl Grignard reagents which have an electron-withdrawing group on the benzene ring, such as the *p*-chloro, *p*-trifluoromethoxy, and *p*-ethoxycarbonyl group, proceeded under optimized conditions to give products **8aG−aI** in moderate to good yields.

Additionally, the sequential reaction of **7a** with aryl Grignard reagents which have *m*-methoxy, *o*-methoxy, *m*,*p*-dimethoxy, and *m*,*m*-dimethoxy groups was also successful (**8aJ−aM**). Heteroaryl groups, including thiophene, furan, benzothiophene, benzofuran, and indole, were also introduced into *N*-alkoxylactam **7a** using the sequential reaction. For example, the heteroarylation of **7a** with heteroaryl lithium reagents proceeded under optimized conditions to afford the corresponding products **8aN−aT** in moderate to good yields. Furthermore, the scope of the sequential reaction using several alkenyl Grignard reagents was investigated and products **8aU** and **8aV** carrying α,β-unsaturated ketone moieties were obtained in moderate yields.[17]

To elucidate the reaction pathway, we indirectly confirmed the formation of chelate intermediate **G** by trapping an electrophile (Scheme 5). By reacting **7a** with PhMgBr followed

Scheme 5. Control experiments



by quenching with acetyl chloride at −78 °C, the *O*-acetylated *N*,*O*-aminal **18** was obtained (eq 1).[18] This result indicates that chelate intermediate **G** is generated *in situ*.[19] To demonstrate the effect of the alkoxy group, the sequential reaction of other lactam types was examined under optimized conditions. The use of *N*-phenethyl lactam **19**, which lacked an oxygen atom compared to *N*-benzyloxylactam **7a**, gave diphenylated *N*,*O*-aminal **20** without the formation of α-benzoylpyrrolidine **21** (eq 2). This result shows that the adjacent nitrogen and oxygen atoms are critical for this nucleophilic addition/ring contraction.[20,21]

Next, the substituent effects of various α-bromo *N*-alkoxylactams with aryl magnesium and heteroaryl lithium reagents were studied (Scheme 6). The sequential reaction of α-bromo lactams **7b−d** with methoxy, allyloxy, and propargyloxy groups at the lactam nitrogen atom provided the desired ring-contracted products **8bA−cN**, **8dA** in good to high yields (entries 1−7). Moreover, the nucleophilic arylation/ring contraction of disubstituted *N*-benzyloxylactams **7e−g** was also examined. The β-methyl group of **7e** significantly affected the reaction, resulting in low yields of the ring-contracted product **8eA** (entry 8). However, when γ- and δ-methyl α-bromo lactams **7f** and **7g** were used, α-acylpyrrolidines **8fA−gN** with various incorporated aryl and heteroaryl groups were obtained in good yields (entries 9−14).

Lastly, the diastereoselective version of this nucleophilic phenylation/ring contraction was investigated by employing a (−)-*cis*-*N*-benzyloxylactam **7g** (Scheme 7). As a result, sequential reaction with PhMgBr proceeded in a stereoselective manner, and desired ring-contracted product **8gA** was obtained with high diastereoselectivity without loss of enantiopurity, thereby indicating that the present method is potentially promising for the synthesis of optically active α-acylpyrrolidines at this stage.

In summary, we have successfully developed a nucleophilic arylation and alkenylation/ring contraction of *N*-alkoxylactams. A variety of Grignard and organolithium reagents including

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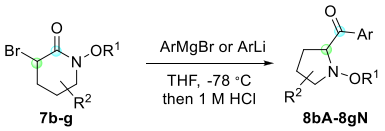
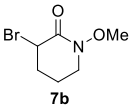
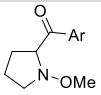
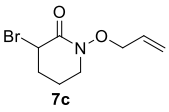
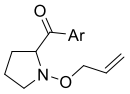
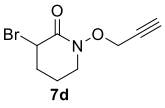
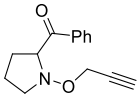
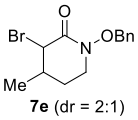
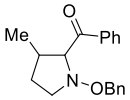
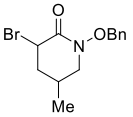
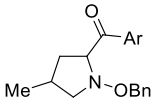
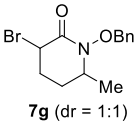
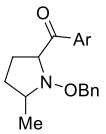
Scheme 6. Substituent Effects of 7b−g with ArMgBr and HetArLi[a]

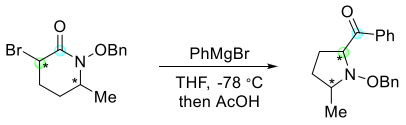


entry	substrate	product	yield (%)[b]
1	 7b		**8bA**: 90 (Ar = Ph)
2			**8bB**: 70 (Ar = *p*-MeOC$_6$H$_4$)
3			**8bN**: 94 (Ar = 5-Me thienyl)[c,d]
4	 7c		**8cA**: 68 (Ar = Ph)
5			**8cB**: 85 (Ar = *p*-MeOC$_6$H$_4$)
6			**8cN**: 95 (Ar = 5-Me thienyl)[c,d]
7	 7d		**8dA**: 52
8	 7e (dr = 2:1)		**8eA**: 14 (dr > 20:1)
9	 7f (dr = 1.5:1)		**8fA**: 65 (Ar = Ph, *cis*:*trans* = 1:1)
10			**8fB**: 72 (Ar = *p*-MeOC$_6$H$_4$, *cis*:*trans* = 2:1)
11			**8fN**: 70 (Ar = 5-Me thienyl, *cis*:*trans* = 1:2)[c,d]
12	 7g (dr = 1:1)		**8gA**: 84 (Ar = Ph, *cis*:*trans* = 2:1)[d]
13			**8gB**: 75 (Ar = *p*-MeOC$_6$H$_4$, *cis*:*trans* = 6:1)[d]
14			**8gN**: 75 (Ar = 5-Me thienyl, *cis*:*trans* = 2:1)[c,d]

[a]Reaction conditions: **7b−g** (0.15 mmol), organometallic reagent (0.30 mmol), THF (2 mL), −78 °C 1−2 h, then 1 M HCl. [b]Yield of the chromatographically pure product. [c]ArLi was *in situ* prepared from ArH and *n*-BuLi (see Supporting Information). [d]The reaction was quenched by AcOH.

aryl, heteroaryl, and alkenyl groups could be utilized in the sequential reaction. As a result, various C(sp^2) units could be introduced to *N*-alkoxylactams, providing various 2-acylpyrrolidines *via* ring contraction. This protocol is a simple procedure in a two-step, one-pot process. This nucleophilic arylation and alkenylation/ring-contractive rearrangement presents a new platform for ring contraction of lactam in organic synthesis.

Scheme 7. Diastereoselective Phenylation/Ring Contraction of (−)-*cis*-7g



Further studies to demonstarate the synthtic utility of the developed methodology, including in the synthesis of biologically active compounds, are now in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03821.

Experimental procedures, and spectroscopic and analytical data for new compounds, including ^{1}H and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 2021279 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(20) Although the ring-opening product has not been obtained to date, the possibility that ring-opening and intramolecular S_N2-type cyclization in the reaction pathway cannot be excluded.

(21) One of the possibilities is that the difference in the reactivities of **7a** and **19** would be attributed to the pyramidalization of the amide functional group.

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