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# Asymmetric Cα-Alkylation of Proline via Chirality Transfers of Conformationally Restricted Proline Derivative: Application to the Total Synthesis of (−)-Amathaspiramide F

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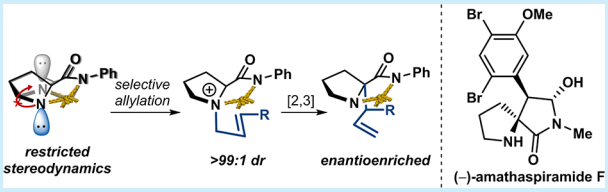
Supporting Information

**ABSTRACT:** An efficient strategy for the asymmetric synthesis of Cα-tetrasubstituted proline derivatives from proline has been established. A nitrogen-fused bicyclic system was devised to control the stereodynamics of proline. Through *N*-quaternizations with allylic electrophiles followed by [2,3]-rearrangements, the bicyclic proline system delivered enantioenriched Cα-tetrasubstituted prolines. This strategy was applied to the concise total synthesis of (−)-amathaspiramide F.

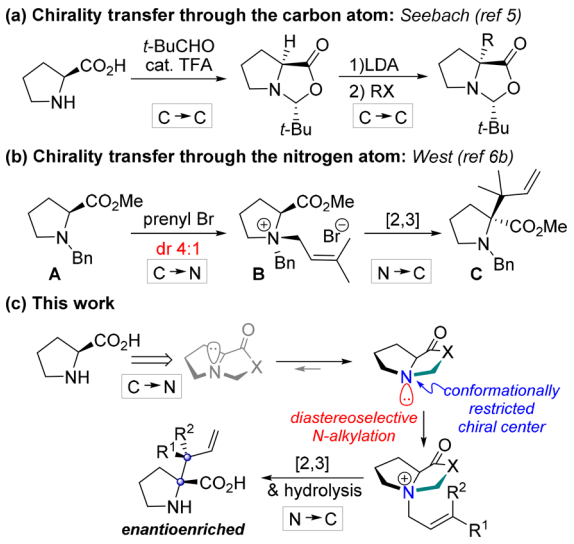





The derivatives of cyclic amino acid proline are of great interest in biology, chemistry, and related fields because proline has a great influence on the structural properties of peptides.[1] Cα-Tetrasubstituted prolines are of particular interest owing to their distinct physicochemical properties including certain conformational features.[2] In addition, they are embedded in the structures of many natural products.[3] Thus, many synthetic strategies have been developed to access these molecules.[4]

Seebach and co-workers achieved the synthesis of Cα-tetrasubstituted prolines from chiral proline itself.[5] Their methodology comprises transferring the chirality of the α-carbon of proline to the newly generated carbon stereocenter (Scheme 1a). In contrast, some approaches utilize transferring the carbon chirality through the nitrogen atom.[6] For example, West and Glaeske[6b] created a temporary chiral center at the nitrogen of proline ester by *N*-quaternization and then installed the Cα-tetrasubstituted stereocenter through a stereospecific rearrangement of the ammonium ylide (Scheme 1b). However, the main shortcoming of this approach was the poor C → N chirality transfer; the diastereomeric ratio of the *N*-quaternization of **A** was only ca. 4:1. Similarly low diastereoselectivities were also observed by several groups in the *N*-quaternization of similar proline substrates.[6c,d]

**Scheme 1. Synthesis of Cα-Tetrasubstituted Prolines**




The low diastereoselectivity of the *N*-quaternization of *N*-substituted proline esters, such as **A**, might be due to the pseudorotational mobility of the pyrrolidine ring system and the low inversion barrier for the nitrogen atom.[7] In most alkyl amines, the activation barriers for pyramidal inversion of $sp^3$-hybridized nitrogen are low (5−9 kcal/mol),[8] and inversion occurs rapidly.[8a,9] Abnormally higher barriers are found for some structurally rigid cyclic amines, such as aziridines[10] or nitrogen-bridged bicycles.[11] For these amines, many theoretical and experimental studies were conducted to reveal the factors that affect the conformational rigidity of the nitrogen atom. However, there are only a few reports that exploit the stereodynamics of an amine for asymmetric synthesis.[8c,12]

We envisioned that the restriction of configurational fluxionality of the proline nitrogen might be one solution in enhancing the diastereoselectivity of the *N*-quaternization of the proline derivative, thereby enabling the asymmetric synthesis of Cα-tetrasubstituted prolines without the aid of external chiral sources via transferring the chirality of the newly generated nitrogen stereocenter to the α-carbon. In this regard, we decided to utilize a nitrogen-fused bicyclic system as shown in Scheme 1c. To our surprise, the configurational fluxionality of nitrogen-fused bicycle has not been seriously questioned.

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Org. Lett. XXXX, XXX, XXX−XXX

As a preliminary model for a proline bicyclic system, an oxazolidinone **1** was considered (Figure 1a). According to our

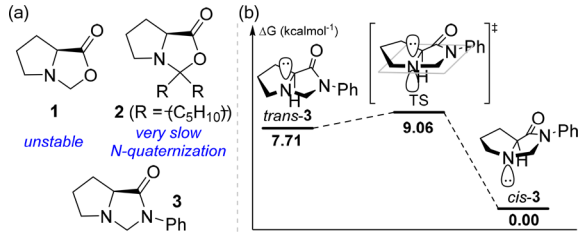
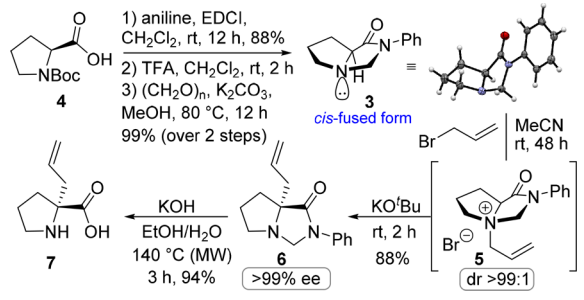



**Figure 1.** (a) Structures of the designed nitrogen-fused bicyclic proline derivatives **1**–**3**. (b) Energy profiles of imidazolidinone derivative **3**. The free energies in MeCN were calculated at the B3LYP/6-31+G(d) level of theory.

calculations, the *cis*-fused form is more stable than the *trans*-isomer and the computed energy barrier of *N*-inversion is high enough (see the Supporting Information (SI)). However, oxazolidinone **1** was not suitable for our purpose because it has been reported to be unstable and easily converted into the zwitterionic iminium species.[13] The corresponding cyclohexanone-derived oxazolidinone **2** is stable,[14] but it was also not adequate because the steric hindrance of the cyclohexyl group would slow the *N*-quaternization. We then turned our attention to imidazolidinone derivative **3**.[15] Our computational studies suggested that the *cis*-fused form of **3** is more stable than the alternative *trans*-isomer (Figure 1b). The energy barrier of *N*-inversion in *cis*-**3** was calculated to be 9.06 kcal/mol, which is high enough to prevent *cis*-to-*trans* isomerization through the inversion of the *N*-chirality (Figure 1b). Thus, the nitrogen atom in *cis*-**3** could be considered a chiral center with its lone pair of electrons located on the convex face of the bicycle. The ensuing *N*-quaternization would occur predominantly from the convex face, and the rearrangement should also occur on the convex face to selectively give C$\alpha$-tetrasubstituted proline derivatives. Herein, we report that the bicyclic proline system **3** imparts complete diastereoselectivity in the formation of a quaternary ammonium intermediate and controls the stereochemical outcome of the [2,3]-Stevens rearrangement[16] to deliver highly enantioselective C$\alpha$-tetrasubstituted proline derivatives from proline as the only source of chirality. In addition, we disclose the total synthesis of amathaspiramide F through the implementation of this synthetic strategy.

The designed bicycle **3** was readily prepared from *N*-Boc-L-proline **4** in three steps in high overall yield (Scheme 2). X-ray crystallography and 2D-NOESY experiments proved that, as expected, **3** exists exclusively in the *cis*-fused form. *N*-

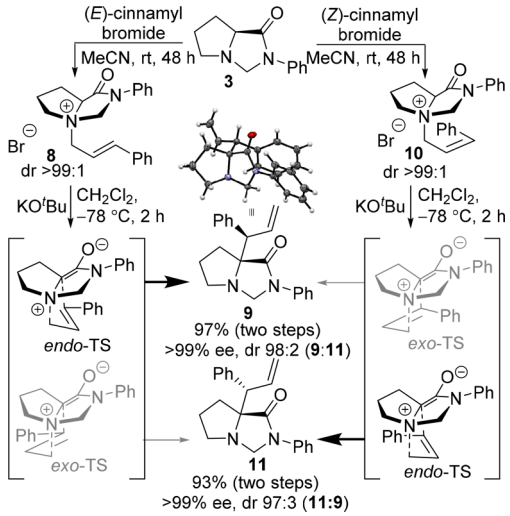
**Scheme 2. Synthesis of Allyl Proline 7 from 4**




Quaternization of **3** was explored using allyl bromide as the electrophile (Scheme 2). The reaction in acetonitrile at room temperature was completely stereoselective and gave the ammonium salt **5** as the only diastereomer. Subsequent in situ addition of KO$^t$Bu gave the $\alpha$-tetrasubstituted proline **6** in high overall yield. The NOESY data revealed that **6** was formed as the *cis*-fused isomer. The enantiopurity of **6**, determined by chiral HPLC analysis, was higher than 99% ee. After hydrolysis of **6** with KOH in aqueous ethanol, its absolute configuration was assigned by comparison of its optical rotation with the known amino acid **7**.[17]

After achieving the highly enantioselective synthesis of $\alpha$-allyl proline **7**, we next focused on the 3-substituted allylic electrophiles that would produce two contiguous stereocenters through an *N*-quaternization/[2,3]-rearrangement reaction sequence. (*E*)-Cinnamyl bromide was initially employed for this purpose. As in the reaction with allyl bromide, *N*-quaternization was completely selective and afforded ammonium salt **8** as the only diastereomer in excellent yield (Scheme 3). The reaction conditions for the rearrangement of

**Scheme 3. Enantio- and Diastereoselective Synthesis of the $\beta$-Substituted $\alpha$-Tetrasubstituted Prolines**




ammonium salt **8** were evaluated, and we found that KO$^t$Bu in $CH_2Cl_2$ at −78 °C was optimal for this transformation, particularly with respect to both yield and diastereoselectivity (see the SI). Under these reaction conditions, the diastereoselectivity of [2,3]-rearrangement of **9** was greater than 98:2 (Scheme 3). The enantiomeric excess of the major tetrasubstituted proline product **9** was greater than 99% ee. The stereochemistry of **9**, determined by X-ray crystallography, suggested that the stereospecific [2,3]-rearrangement proceeded via an *endo* transition state. This *endo* preference might result from the secondary orbital interactions between the anion-stabilizing carbonyl group and the alkene moiety.[18] When (*Z*)-cinnamyl bromide was employed, the tetrasubstituted proline **11** was obtained as the major diastereomer (dr = 97:3). This major diastereomer was the minor product from the reaction with the corresponding (*E*)-substrate. This result demonstrates that by switching the configuration of the double bond both diastereomers of the $\beta$-substituted $\alpha$-tetrasubstituted prolines were accessible via the present strategy.

With the above results in hand, we briefly explored the scope of the reaction (Table 1). All allylic electrophiles examined



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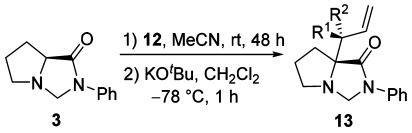
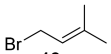
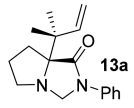
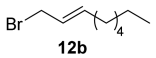
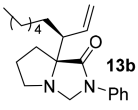
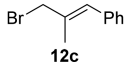
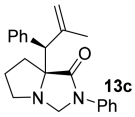
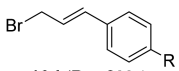
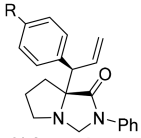
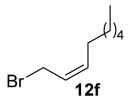
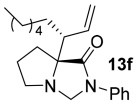
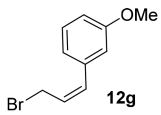
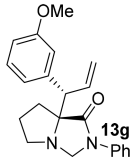
Org. Lett. XXXX, XXX, XXX−XXX

**Table 1. Scope of the Reaction**



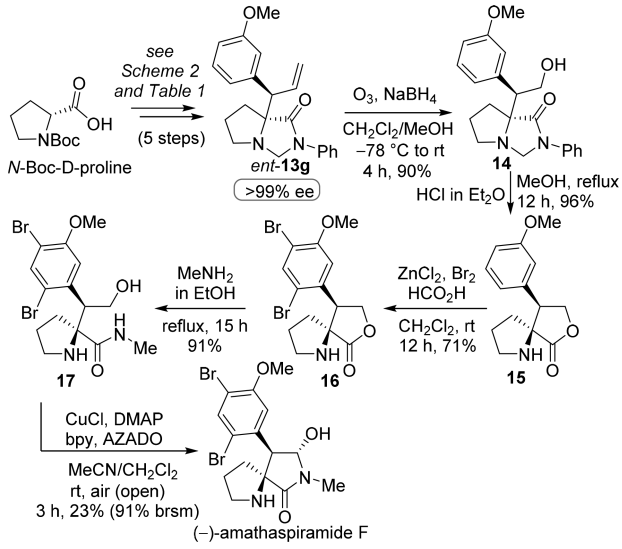

| entry | allylic bromide (**12**) | product (**13**) | yield (%)[a] | dr[b] |
|---|---|---|---|---|
| 1[c] |  **12a** |  **13a** | 79 | - |
| 2 |  **12b** |  **13b** | 81 | 98:2 |
| 3 |  **12c** |  **13c** | 88 | 91:9 |
| 4[c] |  **12d** (R = OMe)<br>**12e** (R = NO$_2$) |  **13d** (R = OMe)<br>**13e** (R = NO$_2$) | **13d**: 95<br>**13e**: 89 | 94:6<br>>99:1 |
| 5 |  **12f** |  **13f** | 65 | 91:9 |
| 6 |  **12g** |  **13g** | 88 | 97:3 |

[a]Yield of isolated product **13** over two steps. [b]The diastereomeric ratio was determined by HPLC. [c]*N*-Quaternization was performed at 40 °C.

herein afforded the desired ammonium salts as single diastereomers, and the corresponding rearrangement products were obtained with higher than 99% ee. *N*-Quaternization with some of the substrates (entries 1 and 4) was sluggish at room temperature, and a higher temperature (40 °C) was required to increase the reaction rate and yield. The diastereoselectivities of the [2,3]-rearrangements were good to excellent, depending on the substituents on the double bond. For example, 3-substituted allylic electrophile **12b** generated a rearranged product **13b** with great diastereoselectivity, while 2,3-disubstituted **12c** led to slightly reduced diastereoselectivity (entry 3). The cinnamyl substrates containing electronically distinct aromatic rings (**12d** and **12e**) were well-behaved in the *N*-quaternization and the rearrangement (entry 4). Allylic electrophiles with *Z*-configurations were also well tolerated and had no significant impact on the diastereoselectivity (entries 5 and 6).

With the strategy for the asymmetric synthesis of $\beta$-substituted $\alpha$-tetrasubstituted prolines successfully established, we applied this method to the total synthesis of amathaspiramide F (Scheme 4). Amathaspiramides are marine alkaloids, and six members of this family have been isolated to date.[19]

**Scheme 4. Total Synthesis of (−)-Amathaspiramide F[a]**




[a]Reagents and conditions: bpy = 2,2′-bipyridine, AZADO = 2-azaadamantane *N*-oxyl.

These compounds share a densely functionalized aza-spirobicyclic core and have three contiguous stereocenters. Due to their intriguing molecular architecture, several groups have synthesized these alkaloids to test new synthetic strategies.[6f,20]

To synthesize the naturally occurring form of (−)-amathaspiramide F, enantiomerically pure *ent*-**13g** (Scheme 4) was prepared from *ent*-**3** in the same manner as shown above (Table 1, entry 6). Ozonolysis and reductive workup with $NaBH_4$ afforded the alcohol **14**. Acid-catalyzed hydrolysis of the imidazolidinone ring was accompanied by cyclization to the corresponding $\gamma$-lactone **15**. The introduction of two bromine atoms to the aromatic ring was achieved following a protocol described by Fukuyama et al.,[20d] which utilized both zinc chloride and formic acid. Aminolysis of the lactone **16** with methylamine in refluxing ethanol provided penultimate intermediate **17**, which was expected to provide amathaspiramide F by oxidizing the hydroxyl group to aldehyde.[21]

Because of the nonproductive or the destructive interaction between the oxidant and the electron-rich unprotected amino group in **17**, typical oxidizing agents failed to provide any of the desired product.[22] The oxidation of the HCl salt of **17** resulted in retro-Mannich fragmentation. Fortunately, Iwabuchi's recently developed aerobic oxidation[23] system consisting of 2-azaadamantane *N*-oxyl (AZADO) and copper(I) was found to facilitate the desired alcohol-selective oxidation in the presence of an unprotected amino group to give amathaspiramide F as a single isomer in 23% yield (91% brsm).[24] The spectral and optical rotation data of the synthetic (−)-amathaspiramide F were in good agreement with those previously reported. Thus, we achieved a concise asymmetric total synthesis of (−)-amathaspiramide F from the commercially available *N*-Boc-D-proline in 10 steps.

In this study, we have successfully developed an enantio- and diastereoselective synthesis of C$\alpha$-tetrasubstituted proline derivatives from proline without the aid of an external source of chirality. Additionally, the developed strategy was utilized in the concise asymmetric total synthesis of (−)-amathaspiramide F. To control the stereodynamics of proline, a proline



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*Org. Lett.* XXXX, XXX, XXX−XXX

imidazolidinone derivative **3** that exists exclusively in the *cis*-fused form was designed. This bicyclic system imparts complete diastereoselectivity in the *N*-quaternization with allylic electrophiles, and this diastereomeric purity was completely transferred via a diastereoselective [2,3]-Stevens rearrangement to give enantiomerically enriched C$\alpha$-tetrasubstituted proline derivatives. Overall, the chiral information on the original $\alpha$-carbon of proline is perfectly transmitted to the adjacent nitrogen center and transferred back to the original carbon center via the rigid bicyclic proline system, which is unique compared to other asymmetric syntheses of C$\alpha$-tetrasubstituted prolines from proline itself. Applications of this method in the synthesis of other natural products and bioactive compounds are in progress and will be reported in due course.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02568.

Experimental procedures, analytical data, and copies of the $^{1}$H and $^{13}$C NMR spectra for all new products (PDF)

### Accession Codes

CCDC 1494921 and 1574039−1574040 contain 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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