OL | Organic Letters

pubs.acs.org/OrgLett Letter

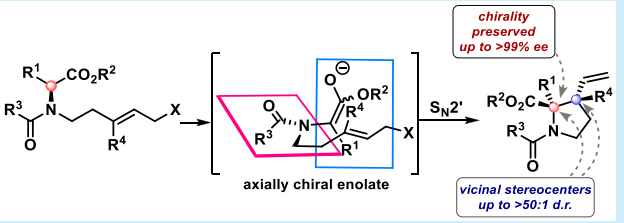
Stereoselective Asymmetric Synthesis of Pyrrolidines with Vicinal Stereocenters Using a Memory of Chirality-Assisted Intramolecular S_N2' Reaction

Jae Hyun Kim, Yundong Chung, Hongjun Jeon, Seokwoo Lee, and Sanghee Kim*

Cite This: https://dx.doi.org/10.1021/acs.orglett.0c01307 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: An efficient strategy for the asymmetric synthesis of pyrrolidines with vicinal quaternary−tertiary or quaternary−quaternary stereocenters was established. A "memory of chirality" intramolecular S_N2' reaction of α-amino ester enolates with allylic halides provided a functionalized pyrrolidine with excellent dia- and enantioselectivity. This method features construction of stereochemically enriched pyrrolidines in a single operation through the influence of a single chiral center presented in substrates.



The stereoselective construction of chiral pyrrolidine rings with multiple stereocenters is a challenging task in organic synthesis.[1] A diverse array of alkaloid natural products and bioactive molecules feature vicinal quaternary−tertiary or quaternary−quaternary stereocenters in the pyrrolidine system (Figure 1).[2] For the enantioselective synthesis of such sterically

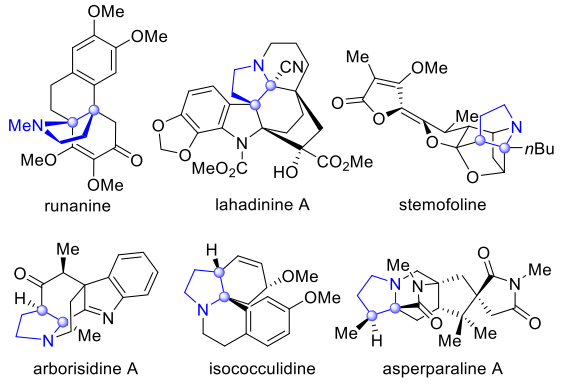
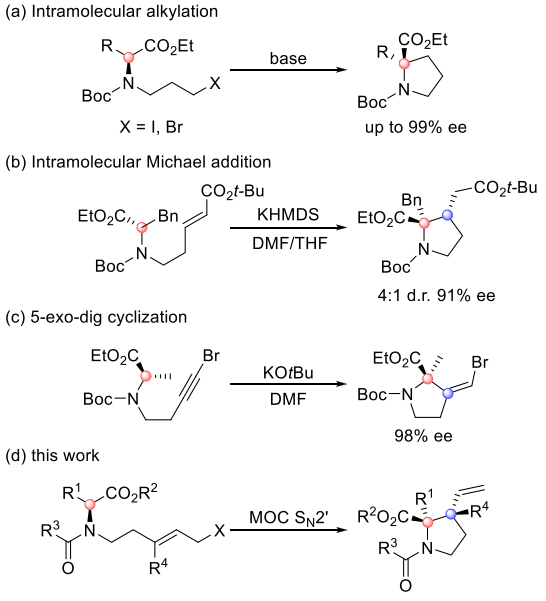


Figure 1. Pyrrolidine natural products featuring vicinal quaternary−tertiary or quaternary−quaternary stereocenters.

demanding structures, considerable progress has been made mainly using the catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides.[1c,d] Other enantioselective approaches has been relatively underdeveloped.

Approaches toward the enantioselective construction of pyrrolidine rings by intramolecular cyclization have attracted a certain degree of attention. One notable approach that has met with success is Kawabata's intramolecular alkylation of α-amino acid derivatives (Scheme 1a)[3] that yielded a pyrrolidine ring with a single quaternary stereocenter, where the chirality of the amino acid is preserved to a high extent via dynamic

Scheme 1. Enantioselective Construction of a Pyrrolidine Ring Using MOC Phenomena



axial chirality of transient enolate intermediates. Kawabata et al. extended this phenomenon of memory of chirality (MOC)[4] to intramolecular conjugated addition reactions to prepare

Received: April 15, 2020

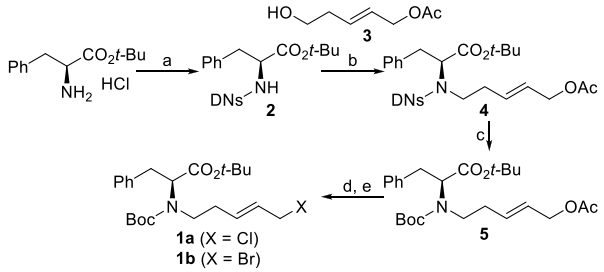
https://dx.doi.org/10.1021/acs.orglett.0c01307
Org. Lett. XXXX, XXX, XXX−XXX

pyrrolidine with vicinal quaternary−tertiary stereocenters (Scheme 1b).[5] The enantiopurity of the obtained products was high (91% ee), while the diastereoselectivity was only modest. Recently, we developed a strategy for the asymmetric 5-exo-dig cyclization of α-amino ester enolates onto heterosubstituted alkynes via the MOC concept (Scheme 1c).[6] This method provided access to the Cα-substituted proline with heterosubstituted methylene at the β-position. This trigonal functionality was eventually transformed into a quaternary stereocenter during the synthesis of hasubanan alkaloids, including runanine (Figure 1).[6a]

Herein, we report the development of an intramolecular MOC S_N2' reaction of acyclic α-amino ester to form pyrrolidines with vicinal quaternary−tertiary or quaternary−quaternary stereocenters (Scheme 1d). This reaction is similar in concept to the previously reported intramolecular MOC alkylations.[3] However, our approach provides value in addition to forming pyrrolidine rings because the intramolecular S_N2' reaction of allylic electrophiles would result in a versatile vinyl functionality and create a new carbon stereocenter generally with excellent stereocontrol because of allylic strain.[7]

To explore the feasibility of this strategy, model substrate **1** was designed (Scheme 2). A Boc group was used as the protecting group on the nitrogen because it is preferable in the generation of an axially chiral amino ester enolate intermediate.[4] Compound **1** was prepared from L-phenylalanine *tert*-butyl ester in five steps without noticeable racemization, as shown in Scheme 2. The introduction of an alkyl substituent on the amino group was realized by Fukuyama−Mitsunobu alkylation.[8] For this, the α-amino group of phenylalanine was first condensed with the 2,4-dinitrobenzenesulfonyl (DNs) group to afford **2**. Under the Mitsunobu reaction conditions, **2** was coupled with (*E*)-5-hydroxypent-2-en-1-yl acetate (**3**). The DNs group was then replaced with the Boc group using a one-pot operation to provide **5**. The acetate group of **5** was removed, and the resulting allyl alcohol was halogenated to provide substrates **1a** and **1b**, which were enantiomerically pure (>99%).

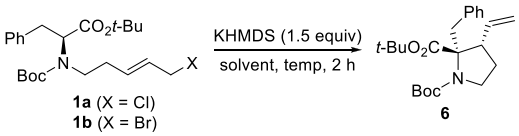
Scheme 2. Representative Scheme for the Synthesis of Substrates 1a and 1b[a]



[a]Reagents and conditions: (a) (i) $NaHCO_3$ (aq), CH_2Cl_2, rt, 1 h; (ii) DNsCl (1.1 equiv), pyridine (3 equiv), CH_2Cl_2, rt, 12 h, 92%; (b) **3** (1.1 equiv), DIAD (1.5 equiv), PPh_3 (2 equiv), benzene, rt, 1 h, 99%; (c) thioglycolic acid (1.5 equiv), Et_3N (3 equiv), CH_2Cl_2, rt, 2 h, then Boc_2O (2 equiv), Et_3N (2 equiv), rt, 48 h, 95%; (d) K_2CO_3 (2 equiv), MeOH, rt, 2 h; (e) PPh_3 (2 equiv), hexachloro-2-propanone (1.5 equiv, for **1a**) or CBr_4 (1.5 equiv, for **1b**), CH_2Cl_2, rt, 2 h, 96% for **1a** (two steps), 97% for **1b** (two steps). DNsCl = 2,4-dinitrobenzenesulfonyl chloride, DIAD = diisopropyl azodicarboxylate.

After several bases and conditions were screened, we obtained a promising result with KHMDS. When the allyl chloride substrate **1a** was treated with KHMDS at −78 °C in THF, the desired S_N2' product **6** was provided in a high yield and dr with 92% ee (Table 1, entry 1). The allyl bromide **1b** furnished product **6** with an enantiopurity higher than that obtained from **1a**, but the diastereoselectivity was much lower (entry 2 vs entry 1). The low diastereoselectivity and instability of the allyl bromide substrate **1b** led us to optimize the reaction conditions with allyl chloride **1a** as a substrate.

Table 1. Optimization of Reaction Conditions[a]



entry	substrate	solvent (0.02 M)	temp (°C)	yield (%)[b]	dr[c]	ee of **6** (%)[d]
1	**1a**	THF	−78	97	19:1	92
2	**1b**	THF	−78	89	6:1	95
3	**1a**	DMF	−60	82	10:1	>99
4	**1a**	THF/DMF (1:1)	−60	93	16:1	>99
5[e]	**1a**	THF/DMF (1:1)	−60	94	14:1	>99

[a]Reactions were run with 0.1 mmol of **1**. [b]Combined yield of **6** and its diastereomer. [c]The ratio was determined by ^1H NMR of the crude mixture. The absolute and relative stereochemistry were tentatively assigned by analogy to **8c**. [d]The enantiomeric excess was determined by chiral HPLC analysis. [e]The reaction was run with 1.0 mmol of **1a**.

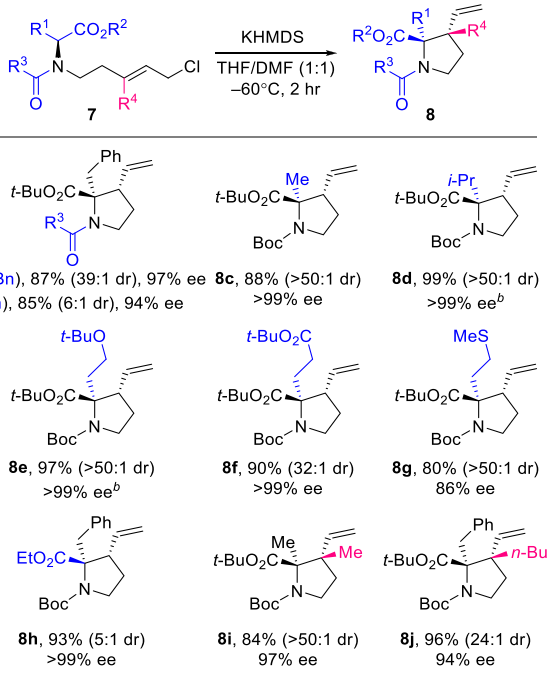
Attempts to optimize the reaction conditions with respect to solvent were conducted. The reaction performed in DMF provided **6** with almost perfect chirality preservation (>99% ee), albeit with diminished diastereoselectivity (entry 3). When the reaction was performed in a THF/DMF mixture (1:1), **6** was obtained with a nearly perfect ee value (>99%) and an excellent dr (16:1) value (entry 4). Applying these conditions to a larger scale reaction led to similar results (entry 5). Additionally, under the conditions of entry 4, the *cis* geometric isomer of **1a** also provided **6** with >99% ee in a slightly lower yield (85%) and diastereoselectivity (10:1).

With the optimized reaction conditions in hand, we explored the substrate scope (Scheme 3). The substrate possessing an *N*-Cbz protecting group underwent the reaction to provide pyrrolidine **8a** with excellent chirality preservation in a significantly increased diastereoselectivity compared to that of *N*-Boc-protected substrate **1a**. The substrate with an *N*-Bz protecting group furnished **8b** with diminished enantio- and diastereoselectivity.

The next exploration of the scope of the reaction under the identified conditions focused on the influence of the α-substituent of α-amino esters on the degree of chirality preservation. With a Boc protecting group, α-amino esters bearing various α-alkyl groups were smoothly cyclized to afford the pyrrolidine products in high yield with excellent ee (**8c**−**8f**). Even substrate **7f** bearing an additional carbonyl group at the γ-carbon afforded product **8f** in high yield with excellent ee. Only **7g**, prepared from methionine, provided product **8g** in diminished yield and ee. Substrate **7h** with the ethyl ester group gave a dr value much lower than that of substrate **1a** with the bulkier *tert*-butyl ester group, suggesting that the bulkiness of the ester group has a significant effect on the diastereoselectivity. Notably, products bearing vicinal quater-

https://dx.doi.org/10.1021/acs.orglett.0c01307
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. Substrate Scope of the MOC S_N2' Reaction[a]

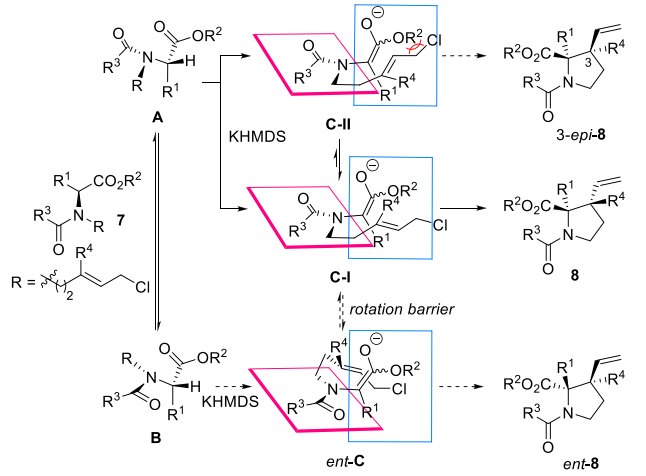


[a]Reactions were run with 0.1 mmol of **7**. The yields shown are isolated yields. The dr values were determined by ^{1}H NMR analysis of the crude mixture. The ee values were determined by chiral HPLC. [b]The ee values were determined after transformation to their *N*-benzoate analogue.

nary–quaternary stereocenters were readily obtained from the trisubstituted allylic substrates in high yield and stereoselectivities (**8i** and **8j**). This result is of particular interest because the alkyl substituent at the R^4 position can retard the S_N2' reaction by several factors such as steric interference with the enolate nucleophile and ground state stabilization of the double bond.[7] To the best of our knowledge, this is the first successful example of applying the concept of MOC alkylation for the formation of vicinal quaternary–quaternary stereocenters with a high level of enantio- and diastereoselectivities.[9]

The absolute configuration of **8c** was determined to be 2*R*,3*S* by the X-ray crystallographic analysis of its *N*-4-bromobenzoate analogue (see the Supporting Information for details). The absolute stereochemistry and relative stereochemistry of **8a**, **8b**, and **8d**–**8j** were tentatively assigned by analogy with **8c**. On the basis of the stereochemical outcome and hypothesis proposed by Kawabata et al.,[3] the mechanism of MOC cyclization was suggested as shown in Scheme 4. The 2*R* configuration indicated that the MOC cyclization occurred with retention of configuration at the Cα-stereogenic center and suggested that the reaction proceeded through axially chiral enolate **C** instead of *ent*-**C**. The formation of enolate **C** by deprotonation of conformer **A** could be more favorable over the formation of *ent*-**C** from conformer **B**, which is another stable conformer of **7**. Deprotonation of **B** would be unfavorable because of the steric interaction between the bulky KHMDS base and the N protecting group as stated previously.[3] Major diastereomer **8** arises from cyclization of enolate conformer **C-I**, which minimizes steric repulsions. The other competing transition conformer **C-II** would experience steric compression between ester enolate and allyl chloride moieties.

Scheme 4. Proposed Mechanism



In conclusion, we have developed an intramolecular MOC S_N2' reaction of acyclic α-amino ester to form pyrrolidines with vicinal quaternary–tertiary or quaternary–quaternary stereocenters. Vicinal stereocenters were installed with excellent dia- and enantioselectivity. Various functional groups were well tolerated. The attraction of this method lies in the asymmetric construction of pyrrolidines with vicinal stereocenters in a single operation through the influence of a single chiral center in the substrate. In addition, the synthetically useful vinyl functionality was introduced into the new stereocenter. Applications of this general methodology to the asymmetric synthesis of complex alkaloids are under investigation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01307.

Experimental procedures, analytical data, chiral HPLC data for compounds **6** and **8**, X-ray crystallographic analysis of the *N*-4-bromobenzoate analogue of **8c**, and copies of the ^{1}H and ^{13}C NMR spectra for all new products (PDF)

Accession Codes

CCDC 1996097 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.

■ AUTHOR INFORMATION

Corresponding Author

Sanghee Kim – *College of Pharmacy, Seoul National University, Seoul 08826, Republic of Korea;* orcid.org/0000-0001-9125-9541; Email: pennkim@snu.ac.kr

Authors

Jae Hyun Kim – *College of Pharmacy, Seoul National University, Seoul 08826, Republic of Korea;* orcid.org/0000-0001-8600-5950

https://dx.doi.org/10.1021/acs.orglett.0c01307
Org. Lett. XXXX, XXX, XXX–XXX

Yundong Chung − *College of Pharmacy, Seoul National University, Seoul 08826, Republic of Korea*
Hongjun Jeon − *College of Pharmacy, Seoul National University, Seoul 08826, Republic of Korea;* orcid.org/0000-0001-5153-5118
Seokwoo Lee − *College of Pharmacy, Seoul National University, Seoul 08826, Republic of Korea;* orcid.org/0000-0002-8309-0624

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c01307

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Mid-Career Researcher Program (NRF-2019R1A2C2009905) of the National Research Foundation of Korea (NRF) funded by the Government of Korea (MSIP).

■ REFERENCES

(1) For selected reviews, see: (a) Pyne, S. G.; Davis, A. S.; Gates, N. J.; Hartley, J.; Lindsay, K. B.; Machan, T.; Tang, M. Asymmetric Synthesis of Polyfunctionalized Pyrrolidines and Related Alkaloids. *Synlett* **2004**, *2004*, 2670−2680. (b) Han, M.-Y.; Jia, J.-Y.; Wang, W. Recent advances in organocatalytic asymmetric synthesis of polysubstituted pyrrolidines. *Tetrahedron Lett.* **2014**, *55*, 784−794. (c) Li, J.; Ye, Y.; Zhang, Y. Cycloaddition/Annulation Strategies for the Construction of Multisubstituted Pyrrolidines and Their Applications in Natural Product Synthesis. *Org. Chem. Front.* **2018**, *5*, 864−892. (d) Adrio, J.; Carretero, J. C. Stereochemical Diversity in Pyrrolidine Synthesis by Catalytic Asymmetric 1,3-Dipolar Cycloaddition of Azomethine Ylides. *Chem. Commun.* **2019**, *55*, 11979−11991.

(2) For selected examples, see: (a) Kongkiatpaiboon, S.; Schinnerl, J.; Felsinger, S.; Keeratinijakal, V.; Vajrodaya, S.; Gritsanapan, W.; Brecker, L.; Greger, H. Structural Relationships of Stemona Alkaloids: Assessment of Species-Specific Accumulation Trends for Exploiting Their Biological Activities. *J. Nat. Prod.* **2011**, *74*, 1931−1938. (b) Hager, A.; Vrielink, N.; Hager, D.; Lefranc, J.; Trauner, D. Synthetic Approaches Towards Alkaloids Bearing α-Tertiary Amines. *Nat. Prod. Rep.* **2016**, *33*, 491−522. (c) Klas, K. R.; Kato, H. J.; Frisvad, C.; Yu, F. S.; Newmister, A.; Fraley, A. E.; Sherman, D. H.; Tsukamoto, S.; Williams, R. M. Structural and Stereochemical Diversity in Prenylated Indole Alkaloids Containing the Bicyclo[2.2.2]diazaoctane Ring System from Marine and Terrestrial Fungi. *Nat. Prod. Rep.* **2018**, *35*, 532−558. (d) Li, C.; Ragab, S. S.; Liu, G.; Tang, W. Enantioselective formation of quaternary carbon stereocenters in natural product synthesis: a recent update. *Nat. Prod. Rep.* **2020**, *37*, 276−292.

(3) (a) Kawabata, T.; Kawakami, S.; Majumdar, S. Asymmetric Cyclization via Memory of Chirality: A Concise Access to Cyclic Amino Acids with a Quaternary Stereocenter. *J. Am. Chem. Soc.* **2003**, *125*, 13012−13013. (b) Kawabata, T.; Matsuda, S.; Kawakami, S.; Monguchi, D.; Moriyama, K. Stereochemical Diversity in Asymmetric Cyclization via Memory of Chirality. *J. Am. Chem. Soc.* **2006**, *128*, 15394−15395. (c) Kawabata, T.; Moriyama, K.; Kawakami, S.; Tsubaki, K. Powdered KOH in DMSO: An Efficient Base for Asymmetric Cyclization via Memory of Chirality at Ambient Temperature. *J. Am. Chem. Soc.* **2008**, *130*, 4153−4157. (d) Moriyama, K.; Sakai, H.; Kawabata, T. Direct Asymmetric Intramolecular Alkylation of β-Alcoxy-α-amino Esters Via Memory of Chirality. *Org. Lett.* **2008**, *10*, 3883−3886.

(4) For reviews on MOC, see: (a) Fuji, K.; Kawabata, T. Memory of Chirality−A New Principle in Enolate Chemistry. *Chem. - Eur. J.* **1998**, *4*, 373−376. (b) Kawabata, T.; Fuji, K. Memory of Chirality: Asymmetric Induction Based on the Dynamic Chirality of Enolates. *Top. Stereochem.* **2003**, *23*, 175−205. (c) Zhao, H.; Hsu, D. C.; Carlier, P. R. Memory of Chirality: An Emerging Strategy for Asymmetric Synthesis. *Synthesis* **2005**, *2005*, 1−16. (d) Patil, N. T. Chirality Transfer and Memory of Chirality in Gold-Catalyzed Reactions. *Chem. - Asian J.* **2012**, *7*, 2186−2194. (e) Campolo, D.; Gastaldi, S.; Roussel, C.; Bertrand, M. P.; Nechab, M. Axial-to-Central Chirality Transfer in Cyclization Processes. *Chem. Soc. Rev.* **2013**, *42*, 8434−8466. (f) Alezra, V.; Kawabata, T. Recent Progress in Memory of Chirality (MOC): An Advanced Chiral Pool. *Synthesis* **2016**, *48*, 2997−3016.

(5) Kawabata, T.; Majumdar, S.; Tsubaki, K.; Monguchi, D. Memory of Chirality in Intramolecular Conjugate Addition of Enolates: a Novel Access to Nitrogen Heterocycles with Contiguous Quaternary and Tertiary Stereocenters. *Org. Biomol. Chem.* **2005**, *3*, 1609−1611.

(6) (a) Tan, S.; Li, F.; Park, S.; Kim, S. Memory of Chirality in Bromoalkyne Carbocyclization: Applications in Asymmetric Total Synthesis of Hasubanan Alkaloids. *Org. Lett.* **2019**, *21*, 292−295. (b) Tan, S.; Li, F.; Park, S.; Kim, S. Carbocyclization of Heterosubstituted Alkynes via the Memory of Chirality: Access to Cα-substituted Proline Derivatives. *J. Org. Chem.* **2019**, *84*, 14436−14450.

(7) (a) Paquette, L. A.; Stirling, C. J. M. The intramolecular S_N' reaction. *Tetrahedron* **1992**, *48*, 7383−7423. (b) Vyas Devambatla, R. K.; Velagaleti, R.; Yarravarapu, N.; Fleming, F. F. S_{Ni}' Displacements with Main Group Organometallics. *Tetrahedron* **2012**, *68*, 2925−2942.

(8) (a) Fukuyama, T.; Jow, C.-K.; Cheung, M. 2- and 4-Nitrobenzenesulfonamides: Exceptionally Versatile Means for Preparation of Secondary Amines and Protection of Amines. *Tetrahedron Lett.* **1995**, *36*, 6373−6374. (b) Kan, T.; Fukuyama, T. Ns Strategies: a Highly Versatile Synthetic Method for Amines. *Chem. Commun.* **2004**, 353−359.

(9) For previous attempts to apply MOC for the formation of two contiguous quaternary stereocenters, see: (a) Giese, B.; Wettstein, P.; Stähelin, C.; Barbosa, F.; Neuburger, M.; Zehnder, M.; Wessig, P. Memory of Chirality in Photochemistry. *Angew. Chem., Int. Ed.* **1999**, *38*, 2586−2587. (b) Resendiz, M. J. E.; Family, F.; Fuller, K.; Campos, L. M.; Khan, S. I.; Lebedeva, N. V.; Forbes, M. D. E.; Garcia-Garibay, M. A. Radical Reactions with Double Memory of Chirality (^{2}MOC) for the Enantiospecific Synthesis of Adjacent Stereogenic Quaternary Centers in Solution: Cleavage and Bonding Faster than Radical Rotation. *J. Am. Chem. Soc.* **2009**, *131*, 8425−8433. (c) Mondal, S.; Nechab, M.; Campolo, D.; Vanthuyne, N.; Bertrand, M. P. Copper Carbenoid, Reactant and Catalyst for One-Pot Diazo Ester Coupling Cascade Rearrangement of Enediynes: Formation of Two Contiguous Tetrasubstituted Stereocenters. *Adv. Synth. Catal.* **2012**, *354*, 1987−2000. (d) Kim, J. H.; Lee, S.; Kim, S. Biomimetic Total Synthesis of (−)-Penibruguieramine A Using Memory of Chirality and Dynamic Kinetic Resolution. *Angew. Chem., Int. Ed.* **2015**, *54*, 10875−10878. (e) Yang, P.; Yoshimura, T.; Sasamori, T.; Tokitoh, N.; Morisaki, K.; Kawabata, T. Protonation-Assisted Conjugate Addition of Axially Chiral Enolates: Asymmetric Synthesis of β-Lactams with Contiguous Tetrasubstituted Stereocenters from α-Amino Acids via Memory of Chirality. *Heterocycles* **2020**, *101*, 664−678.

https://dx.doi.org/10.1021/acs.orglett.0c01307
Org. Lett. XXXX, XXX, XXX−XXX