Organic & Biomolecular Chemistry

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Journal:	*Organic & Biomolecular Chemistry*
Manuscript ID	OB-COM-11-2024-001815.R1
Article Type:	Communication
Date Submitted by the Author:	18-Jan-2025
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COMMUNICATION

Chemodivergent Synthesis of *cis*-4-Hydroxyprolines from Diastereomerically Enriched Epoxides

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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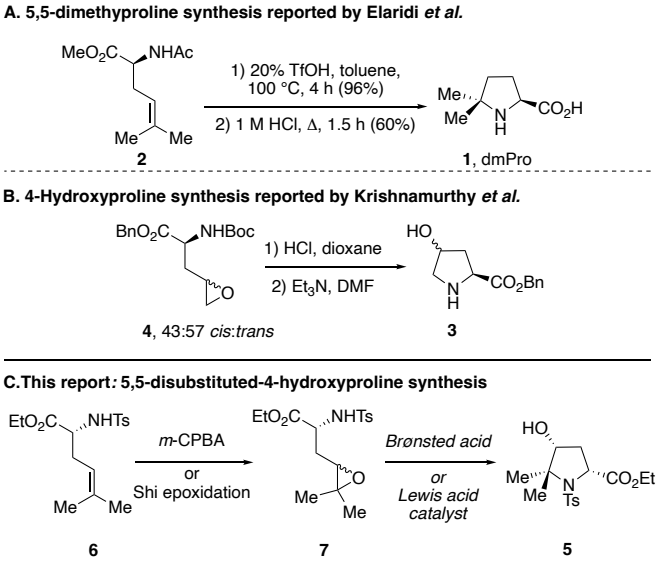
A method for synthesis of *cis*-4-hydroxyproline analogs is described. A *cis* epoxide is converted to a *cis*-4-hydroxyproline, while the *trans* epoxide is converted into a ketone or α-aminolactone in the presence of Lewis and Brønsted acids. We propose the divergent chemoselectivity is controlled by H-bonding within the *cis* epoxide.

Introduction

Substituted prolines are a prevalent motif found in numerous natural products, including cyclopiazonic acid and related alkaloids.[1] 5,5-Dimethylproline (dmPro, **1**, Scheme 1A) in particular has attracted considerable attention among organic chemists, due to the tendency for the *gem*-dimethyl group to lock peptides in the non-native *cis* conformation, which has a dramatic impact on protein folding.[2] Although a number of methods have been reported for preparing proline analogs with substitution at the 5-position,[3] as well as the 4-position,[4,5] few methods exist for producing analogs substituted at both positions.[6] 4-Hydroxyprolines (Hyp) are generally prepared biosynthetically,[7] while **1** is synthesized through a cationic cyclization of a dimethylallylglycine precursor (e.g. **2**, Scheme 1A).[3] Knight and co-workers have reported several procedures for accessing 4-iodoprolines and 4-phenylselenoprolines with substitution at the 5-position,[8] however, this methodology has not been extended to include synthesis of 4-hydroxyprolines with similar substitution patterns. A previous report described the synthesis of Hyp derivative **3** by epoxidation of *N*-Boc-allylglycine methyl ester, providing epoxide **4** as a mixture of *cis*:*trans* isomers with subsequent Boc-deprotection and cyclization of the nitrogen to form the pyrrolidine ring (Scheme 1B).[7c] We envisioned combining this epoxidation and cyclization approach, using a sulfonamide cyclization to form 4-hydroxy-5,5-dimethylproline derivatives (such as **5**, Scheme 1C), in which a Brønsted or Lewis acid catalyst would be used to promote the cyclization. Herein we describe a method for synthesis of 5,5-disubstituted-*cis*-4-hydroxyprolines, which are obtained as single diastereomers (>98:2 d.r. based on ^{1}H NMR spectral data). To the best of our knowledge there are no previous reports of methods for synthesizing prolines with this substitution pattern.

Scheme 1. Prior methods for 4- and 5-substituted proline synthesis



Results and discussion

Our approach began by preparation of (±)-dimethylallyl-Gly **6** by Ru-catalyzed olefin cross metathesis,[3b] followed by oxidation of the trisubstituted alkene by *m*-CPBA, furnishing epoxide **7** as a

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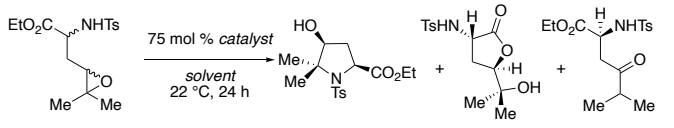
† Electronic supplementary Information (ESI) available. CCDC numbers: 2385171-2385173, 2386128. See DOI: 10.1039/x0xx00000x

49:51 *cis*:*trans* mixture of racemic stereoisomers, which were inseparable by chromatography (Scheme 1C). Based on previous reports describing nucleophilic attack of sulfonamides on epoxides,[9] we decided to employ *p*-toluenesulfonic acid (*p*-TsOH) as a catalyst. When epoxide **7** was stirred in toluene for 24 hours in the presence of 75 mol% *p*-TsOH the desired *cis* hydroxyproline (**5**) was observed by ^{1}H NMR in 22% conv[10] (Table 1, entry 2).

Table 1. Screening conditions for synthesis of proline **5**



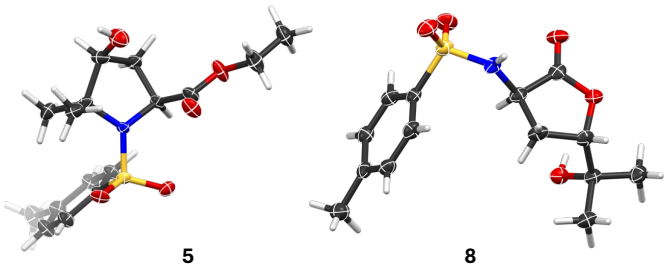
(±)-**7** (49:51 d.r. *cis*:*trans*) (±)-**5**, *cis*-proline >98:2 d.r. *cis*:*trans* (±)-**8**, *trans*-lactone >2:98 d.r. *cis*:*trans* (±)-**9**, ketone

entry	catalyst	solvent	%**5**[a]	%**8**[a]	%**9**[a]
1[b]	none	toluene	4%	3%	0%
2	*p*-TsOH	toluene	22%	23%	5%
3	*p*-TsOH	MeCN	17%	32%	3%
4	*p*-TsOH	CH_2Cl_2	21%	28%	5%
5	*p*-TsOH	EtOH	11%	18%	4%
6	TfOH	CH_2Cl_2	29%	6%	32%
7[c]	TfOH	CH_2Cl_2	31%	19%	9%
8	TFA	CH_2Cl_2	23%	10%	11%
9	$HClO_4$	CH_2Cl_2	29%	12%	9%
10	H_2SO_4	CH_2Cl_2	17%	3%	13%
11[c]	$InCl_3$	CH_2Cl_2	25%	25%	13%
12[c]	$InBr_3$	CH_2Cl_2	29%	27%	16%
13[c]	$In(OTf)_3$	CH_2Cl_2	28%	31%	3%
14[c]	$La(OTf)_3$	CH_2Cl_2	27%	32%	4%
15[c]	$Zn(OTf)_2$	CH_2Cl_2	27%	14%	4%

[a] % conv based on ^{1}H NMR using a 1,2,3-trimethoxybenzene internal standard, calculated based on the total mmol of the epoxide mixture; [b] 80 °C; [c] 10 mol % catalyst.

Although we expected the proline to be obtained as a mixture of *cis* and *trans* isomers, to our surprise we did not detect any *trans*-4-hydroxyproline by ^{1}H NMR. Instead, we observed 23% conv to a new compound, *trans*-α-aminolactone **8**,[11] presumably derived from the *trans*-epoxide, along with 5% conv to ketone **9**, which would be the product of a House-Meinwald rearrangement (Table 1, entry 2).[12] This result is notable as it is normally the case that a mixture of diastereomers will be converted into diastereomeric products, instead of each diastereomer undergoing a different chemical reaction.[13] In the absence of catalyst at 80 °C, only very low conversion was observed (4% conv to **5**, 3% conv to **8**, Table 1, entry 1). We screened a wide range of conditions for the reaction, including several different solvents, such as acetonitrile, dichloromethane, and ethanol (Table 1, entries 3-5). Acetonitrile improved conversion to lactone **8**, and dichloromethane gave the highest overall conversion to the three products. In the presence of trifluoromethanesulfonic acid (TfOH), conversion to *cis*-proline was slightly improved (29% conv to **5**, Table 1 entry 6, as compared to 21% with *p*-TsOH), and in contrast to other Brønsted acids screened, TfOH also produced 32% conv to ketone **9** (compared to 5% with *p*-TsOH in CH_2Cl_2). Reducing the catalyst loading for TfOH from 75 mol % to 10 mol % left the overall conversion roughly unchanged but favored formation of lactone **8** over the ketone **9** (Table 1, entry 7). This suggests that the rate of hydrolysis of the epoxide, which likely precedes lactonization, becomes competitive with House-Meinwald rearrangement at lower acid concentration. While $HClO_4$ produced a similar amount of proline **5** compared to TfOH, trifluoroacetic acid (TFA) and H_2SO_4 were both inferior (Table 1, entries 8-10). We next examined whether Lewis acid catalysts were also capable of promoting the reaction, and found that 10 mol % $InCl_3$ and $InBr_3$ both promoted the cyclization to form *cis*-proline **5** with comparable efficiency to TfOH (Table 1, entries 11-12). Other Lewis acids (including $In(OTf)_3$, $La(OTf)_3$, and $Zn(OTf)_2$) all promoted the reaction as well, but favored formation of lactone **8** over ketone **9** (Table 1, entries 13-15).

Figure 1. Single-crystal X-ray diffraction structures of **5** and **8**

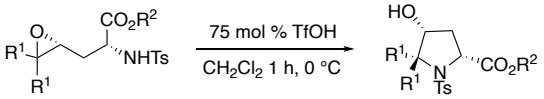


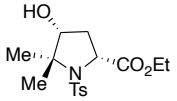
5 **8**

While ^{1}H NMR analysis revealed that both proline **5** and lactone **8** were obtained in >98:2 d.r., the relative stereochemistry of compounds **5** and **8** was determined by single crystal X-ray diffraction (Figure 1). Crystallographic analysis confirmed that proline **5** was the *cis* isomer, which crystallized in the monoclinic space group $P2_1/c$ in a C_γ-endo pucker, in which the ring twists to place the γ-carbon in close proximity to the ester.[14] Lactone **8** was isolated exclusively as the *trans* isomer, and crystallized in two forms (i.e. $P2_1/c$ and $Pna2_1$ polymorphs). In the $P2_1/c$ polymorph, molecules of **8** form hydrogen-bond dimers with the O-H group and neighboring sulfonamide groups. In the $Pna2_1$ polymorph, the O-H group supports dimers via H-bonds with an adjacent lactone ring (see the Supporting Information for details). We hypothesized that the proportion of ketone and lactone produced by the Lewis acid catalysts may be controlled by varying amounts of moisture present in these highly hygroscopic compounds. To test this hypothesis, the 49:51 *cis*:*trans* epoxide racemic mixture was subjected to $InBr_3$ inside a glovebox with oven dried 4 Å molecular sieves added to the mixture. In this case, proline **5** is obtained in 32% yield, along with 38% yield of ketone **9**, and lactone **8** was not detected by ^{1}H NMR. This demonstrates that formation of lactone **8** requires water, suggesting that the epoxide likely undergoes hydrolysis prior to lactonization. To improve the yield of the proline reaction, we sought to selectively generate the *cis* epoxide. Using the *D*-fructose-derived Shi catalyst to epoxidize the (2*R*)-alkene **6** (Scheme 1C), we obtained an 89:11 (2*R*,4*R*)-*cis*:(2*S*,4*R*)-*trans* diastereomeric mixture.[15,16] The observed selectivity is typical for unactivated trisubstituted alkenes using the Shi epoxidation.[15] We also attempted epoxidation using the

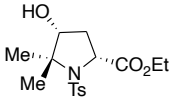
Jacobsen catalyst, but <2% conv to epoxide was observed.[17] Unfortunately, the diastereomerically enriched epoxide led to only a modest increase in proline yield (Scheme 2). When an 89:11 (2*R*,4*R*)-*cis*:(2*S*,4*R*)-*trans* mixture of epoxide **7** was treated with 75 mol % TfOH in CH_2Cl_2, after 1 hour at 0 °C, proline (2*R*,4*R*)-**5** was obtained in 55% conv, 53% yield. This is a marked improvement compared with 28% conv and 27% yield of racemic *cis*-**5** obtained from the 49:51 *cis*:*trans* racemic mixture of epoxide **7**.Interestingly, 22% ketone was also obtained from the 89:11 *cis*:*trans* mixture, suggesting that House-Meinwald rearrangement can proceed both from the *trans* and *cis* epoxides, even though the *cis* epoxide preferentially forms proline **5**. Ketone (2*S*)-**9** and lactone (2*S*,4*R*)-**8** could also be isolated from epoxide mixtures enriched in the *trans* epoxide isomer, synthesized from (2*S*)-alkene **6**. Upon treatment with 10 mol % $La(OTf)_3$ in anhydrous CH_2Cl_2, a 15:85 (2*S*,4*S*)-*cis*:(2*S*,4*R*)-*trans* epoxide mixture furnished lactone (2*S*,4*R*)-**8** in 47% conv, 44% yield. In the presence of 10 mol % $InBr_3$ (under rigorously anhydrous conditions in the glovebox), ketone (2*S*)-**9** could be obtained from the same epoxide mixture in 45% conv, 42% yield.

Scheme 2. Substrate scope for the epoxide opening reaction

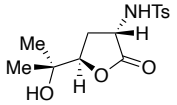




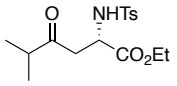
a) epoxide d.r. 89:11 *cis*:*trans*
(2*R*,4*R*)-**5**, 55% conv, 53% yield[a]
b) epoxide d.r. 49:51 *cis*:*trans*
(±)-**5**, 29% conv, 27% yield[b]



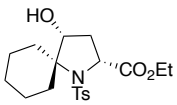
(with 10 mol % $InBr_3$)
epoxide d.r. 89:11 *cis*:*trans*
(2*R*,4*R*)-**5**, 46% conv, 42% yield[c]



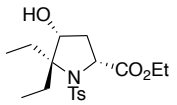
(with 10 mol % $In(OTf_3)$)
epoxide d.r. 15:85 *cis*:*trans*
(2*S*,4*R*)-**8**, 47% conv, 44% yield[d]



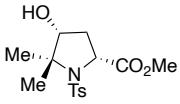
(with 10 mol % $InBr_3$)
epoxide d.r. 15:85 *cis*:*trans*
(2*S*)-**9**, 45% conv, 42% yield[c]



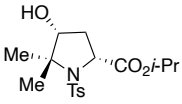
epoxide d.r. 91:9 *cis*:*trans*
(2*R*,4*R*)-**10**, 56% conv, 55% yield



epoxide d.r. 88:12 *cis*:*trans*
(2*R*,4*R*)-**11**, 39% conv, 37% yield



epoxide d.r. 89:11 *cis*:*trans*
(2*R*,4*R*)-**12**,56% conv, 51% yield



epoxide d.r. 89:11 *cis*:*trans*
(2*R*,4*R*)-**13**, 62% conv, 57% yield

[a] 24% conv, 22% yield to ketone **9**; [b] 40% conv, 37% yield of ketone **9**; [c] 10 mol % $InBr_3$, 4 Å MS, CH_2Cl_2, 3 h, 22 °C; [d] 10 mol % $In(OTf)_3$, CH_2Cl_2, 24 h, 22 °C; % conv based on ^1H NMR using a 1,2,3-trimethoxybenzene internal standard, calculated based on the total mmol of the epoxide mixture.

With anhydrous $InBr_3$, the 89:11 (2*R*,4*R*)-*cis*:(2*S*,4*R*)-*trans* mixture of epoxide **7** provides diminished results compared to the TfOH-catalyzed conditions, furnishing (2*R*,4*R*)-**5** in 46% conv, 42% yield. In addition, we examined different epoxide substrates, derived from symmetrical trisubstituted olefins by the same Ru-catalyzed cross metathesis as the parent substrate **6** (Scheme 2, prolines (2*R*,4*R*)-**10** and (2*R*,4*R*)-**11**).[18,19] For spirocycle (2*R*,4*R*)-**10**, a 91:9 (2*R*,4*R*)-*cis*:(2*S*,4*R*)-*trans* epoxide mixture provides the proline product in 56% conv, 55% yield. Production of 5,5-diethylproline **11**, however, was less efficient, producing only 39% conv, 37% yield of the proline from an 88:12 (2*R*,4*R*)-*cis*:(2*S*,4*R*)-*trans* epoxide mixture. The reduced efficiency for the latter reaction is likely due to the enhanced steric bulk at the δ-carbon. We also examined modification of the ester substituent, and found that methyl ester (2*R*,4*R*)-**12** was obtained in similar yield to the ethyl substrate (56% conv, 51% yield).

Figure 2. Epoxide substrates unstable to chromatography

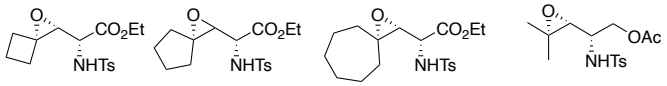
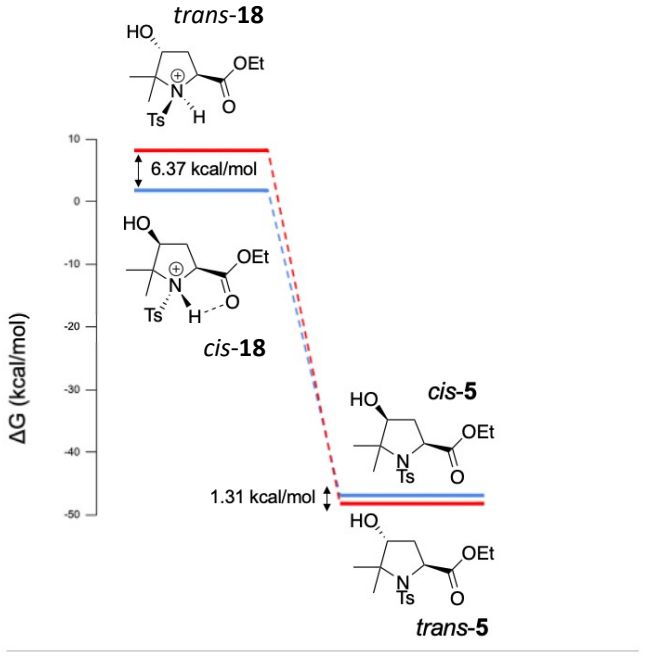
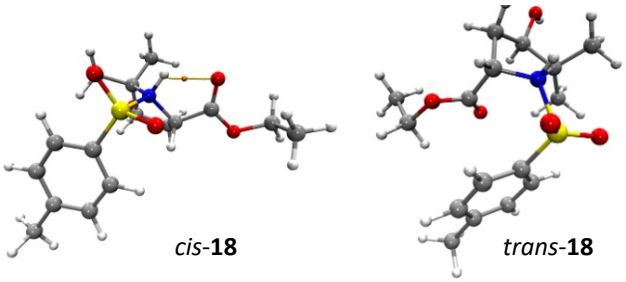


Figure 3. Thermochemical analysis of reaction intermediates leading to the *cis*-**5** and *trans*-**5** products

A. Key intermediates in proline synthesis



B. H-bonding in *cis*-18



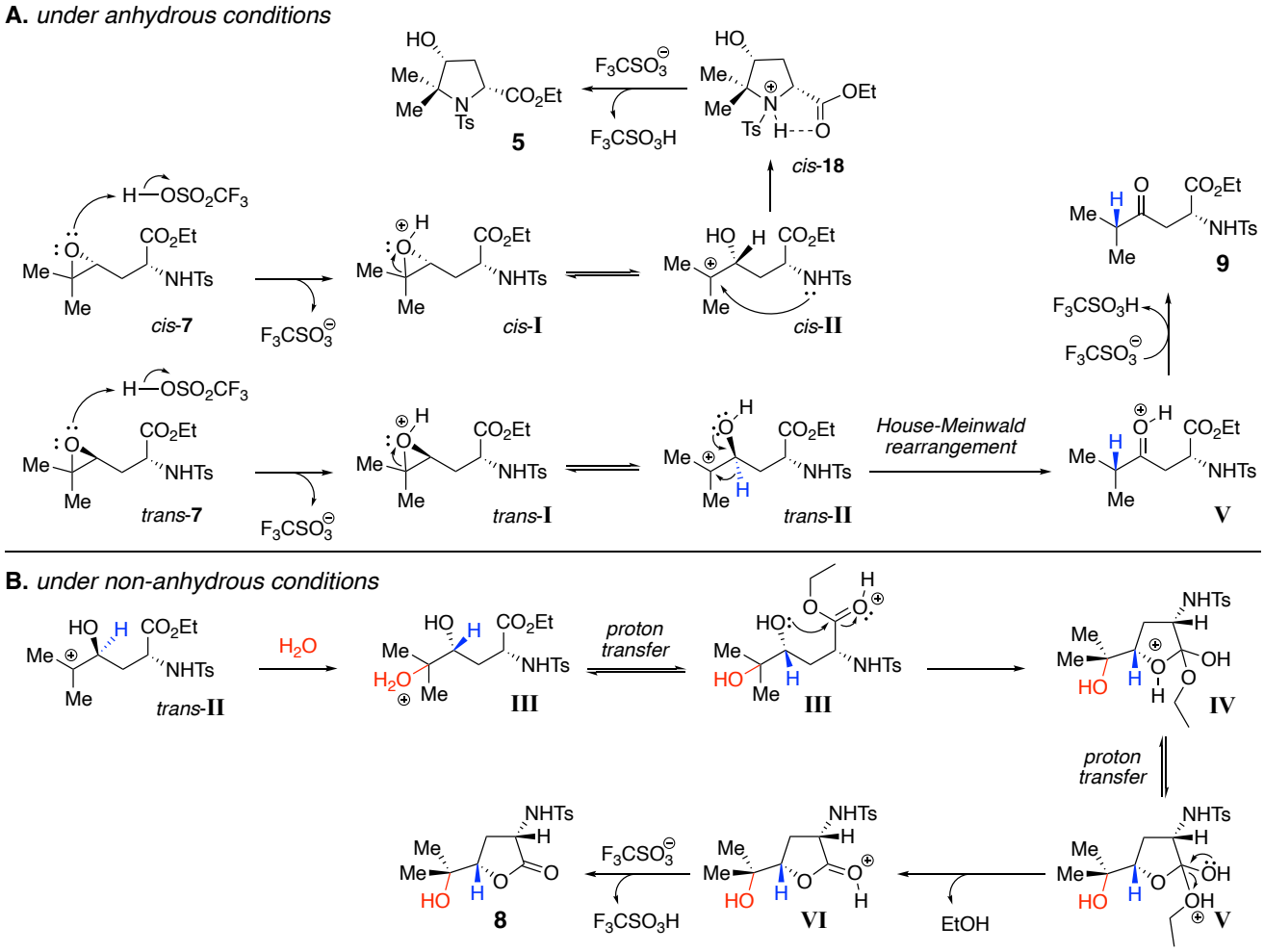
Increasing the steric bulk to an isopropyl group did not diminish the yield either, as proline (2*R*,4*R*)-**13** was obtained in 62% conv, 57% yield.

The observed yields for all five new prolines are moderate in part because the products are generated as a mixture. Mixtures of products and moderate yields are generally considered undesirable in synthesis, but in this case they are part of a useful strategy,[13] as an intractable mixture of diastereomers is converted into an easily separable mixture of products that includes the desired product as a single stereoisomer (>98:2 d.r. based on ^{1}H NMR spectral data). Given the propensity of sulfonamides to undergo intermolecular epoxide opening reactions,[9a,9b] it is also possible the low yields observed in this reaction are partially due to oligomerization of the epoxide.

We examined several other symmetrical trisubstituted alkenes in the Shi epoxidation (Figure 2), including ones derived from methylenecyclobutane (**14**), methylenecyclopentane (**15**), and methylenecycloheptane (**16**). However, each of these epoxides proved to be unstable to purification on silica gel, basic alumina, and Florisil® and we were therefore not able to evaluate the epoxide opening reaction for these substrates. We also prepared a substrate in which the ester was reduced to an alcohol and then protected as an acetate (**17**), however, the epoxide also decomposed during attempted purification. In principle, unsymmetrical trisubstituted alkenes could be employed, but this introduces the additional challenge of controlling *E*:*Z* selectivity during cross metathesis; previous reports indicate that *E*:*Z* selectivity is moderate at best for Ru-catalysts (2.3:1 to 4:1 *E*:*Z*).[19]

Given the unusual chemodivergent outcome of the epoxide opening, we calculated the relative free energies for plausible protonated proline intermediates *cis*-**18** and *trans*-**18**, as well as the deprotonated proline products *cis*-**5** and *trans*-**5** (Figure 3A), using DFT (B3LYP, 6-311G+(d,p), see Supporting Information for details).[20] For the proline product **5**, the *trans* isomer was found to be slightly thermodynamically favored relative to the *cis* isomer (by 1.31 kcal/mol), while for the protonated proline intermediate **18**, the *cis* isomer was favored (by 6.37 kcal/mol). We propose that the stabilization of *cis*-**18** is caused by a H-bond between the sulfonamide N-H proton and the carbonyl oxygen of the ester, the presence of which we confirmed by QTAIM (Figure 3B).[21] For structure *trans*-**18**, the orientation of the ester is positioned *syn* to the N-Ts group, making it geometrically impossible for a H-bond to be present. We propose that the stabilization of intermediate *cis*-**18** relative to *trans*-**18** causes product **5** to be obtained as a single diastereomer.

Scheme 3. Possible mechanism



In light of our experimental data and computational investigation, we propose a possible catalytic mechanism to account for the observed products (Scheme 3). We have illustrated the case of epoxides cis-**7**

and *trans*-**7** with TfOH as the catalyst. First, protonation of the epoxide forms cationic intermediates *cis*-**I** and *trans*-**I**. Ring-opening generates carbocations *cis*-**II** and *trans*-**II**, which are common intermediates for all three observed pathways. In the case of *cis*-**II**, the favorable H-bonding interaction between the ester and sulfonamide N-H lowers the energy barrier sufficiently to allow nucleophilic attack by the sulfonamide nitrogen, closing the pyrrolidine ring to form intermediate *cis*-**18**. The TfOH is then regenerated by deprotonation of *cis*-**18**, providing *cis*-proline **5**. In the case of *trans*-**II**, since there is no favorable H-bonding interaction capable of lowering the barrier to proline formation, intermediate *trans*-**II** undergoes House-Meinwald rearrangement to form protonated ketone **V**, and after regeneration of TfOH, ketone **9**. Under non-anhydrous conditions, *trans*-**II** can alternatively be trapped by water, forming the corresponding protonated diol **III**, which can then cyclize to form intermediate **IV**. After proton transfer (forming intermediate **V**), elimination of ethanol leads to formation of protonated lactone **VI**. Following regeneration of TfOH, lactone **8** is obtained. As the *cis* isomer of lactone **8** is not observed, we propose that lactonization kinetically outcompetes the House-Meinwald path for the *trans* substrate but not the path to proline formation for the *cis* substrate. In the case of the Lewis-acid catalyzed variant, all pathways would be similar, and the Lewis-acid would replace the oxygen-bound proton in the formation of intermediate **I**.

Conclusions

In conclusion, we have developed the first synthetic route for accessing *cis*-4-hydroxyproline analogs bearing two alkyl substituents at the 5-position, and we report the synthesis of the first five synthetic prolines of this type. An unusual feature of the synthesis is that a mixture of diastereomers is transformed into an easily separable mixture that includes the desired product as a single stereoisomer. Given the dearth of methods for synthesizing prolines with the substitution pattern reported here, we believe this is a valuable new approach to proline synthesis that will have applications in the synthesis of a variety of peptides and natural products.

Acknowledgments

We gratefully acknowledge financial support from the M. J. Murdock Charitable Trust (NS-202222588), Reed College, and the following undergraduate fellowships: Moore Fellowship (K. C. Bhatt and O. Pope), Geselbracht Fellowship (Z. Kamanya), Scott/Cronyn Fellowship (H. Doherty, O. Pope), Cronyn Fellowship (G. Mauk, H. Doherty, M. Ongbongan), and the Reed College Science Research Fellowship (H. Doherty, L. Forshee). The material is based upon work supported by the National Science Foundation under Grant No. CHE-2319929. We also acknowledge the Department of Chemistry at Willamette University and the Mass Spectrometry Lab, School of Chemical Sciences at the University of Illinois Urbana-Champaign for analytical services. This work used Bridges-2 at the Pittsburgh Supercomputing Center (PSC) through allocation CHE200095 from the Advanced Cyberinfrastructure Coordination Ecosystem: Services & Support (ACCESS) program,[22] which is supported by National Science Foundation grants #2138259, #2138286, #2138307, #2137603, and #2138296.

Conflicts of interest

There are no conflicts to declare.

Data availability

The ^{1}H NMR, ^{13}C NMR, IR, HPLC, optical rotations, and X-ray crystallographic data underlying this study are available in the in the ESI.†

Notes and references

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Data Availability Statement

The ^{1}H NMR, ^{13}C NMR, IR, HPLC, optical rotations, and X-ray crystallographic data underlying this study are available in the in the ESI.

All .cif files for proline **5**, lactone **8** ($Pna2_1$), lactone **8** ($P2_1/c$), and ketone **9** have been deposited in the Cambridge Crystallographic Data Center (CCDC 2385171, 2385172, 2385173, 2386128), and have been included with this submission.