Organic LETTERS

Letter

pubs.acs.org/OrgLett

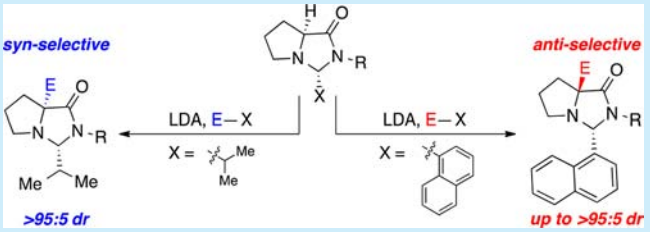
Complementary Stereochemical Outcomes in Proline-Based Self-Regenerations of Stereocenters

Brian J. Knight, Erin E. Stache, and Eric M. Ferreira*

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523, United States

Supporting Information

ABSTRACT: Stereoselective alkylations of proline-based amino amides are described, where high levels of either a *cis* or *trans* configuration can be attained simply by the choice of the aminal group. Isobutyraldehyde-derived aminals provide the *cis* configuration, while 1-naphthaldehyde-derived aminals engender the complementary *trans* configuration.



α-Quaternary proline-based amino acids and their derivatives are important compounds owing to their applications as synthetic building blocks and in peptide studies, among several other areas.[1−3] One of the most reliable processes for accessing this structural motif in enantioenriched form is the self-regeneration of stereocenters (SRS).[4,5] This strategy entails installing a temporary substituent and then using it to govern diastereoselection in a subsequent alkylation process. Stereoselectivity has generally been attributed to a steric influence of this substituent. We hypothesized that these reaction manifolds may be dictated by specific characteristics of the temporary group, and in turn this idea could lead to complementary modes of selectivity. Herein, we illustrate this principle in the context of α-quaternary amino amide synthesis, where we can select for opposing alkylation stereoselectivities by simply changing the nature of the imidazolidinone substituent.

In Seebach's self-regeneration of stereocenters with proline,[5] an *N,O*-acetal based on pivalaldehyde is generated, and alkylation occurs from lithium enolate **2** to form acetal **3** (Figure 1). A 1,3-*syn* relationship between the *tert*-butyl and the alkylating agent is observed, originating from the preference of the bulky *t*-Bu group to be situated on the convex face of the bicyclic system. Further developments in this methodological approach have been reported,[6] as well as wide exploitation in several areas of study.[2,3,6b] An interesting reversal of stereoselectivity, based on structurally similar amino *amides*, was reported by Trauner in the combination of silyl enol ethers with nitroolefins (Figure 1, **4** → **6**).[7] Considering this prior art and given our interest in proline-based amino amides for the design of ligands for palladium-catalyzed C−H bond functionalizations,[8] we appreciated the importance of confirming the stereochemical configuration that can arise from these alkylation processes.[9]

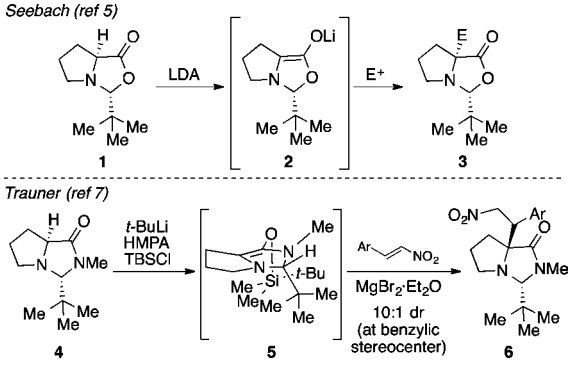
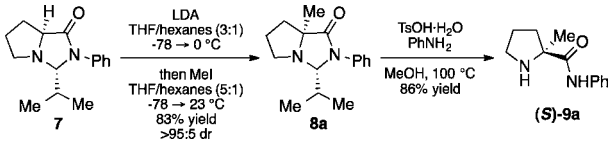


Figure 1. Proline-based self-regeneration of stereocenters.

To that end, we evaluated the reactivity of imidazolidinone **7** (Scheme 1), derived from the phenyl amide of proline and isobutyraldehyde.[10] Alkylation using LDA and MeI produced compound **8a**, again as a single diastereomer. Cleavage of the imidazolidinone[8] afforded amino amide **9a** with the absolute configuration depicted (*S*).[11] The stereochemistry of the alkylation was therefore consistent with the facial selectivity of Seebach's work,[5] in that the electrophile added in a *syn* fashion relative to the isopropyl group.

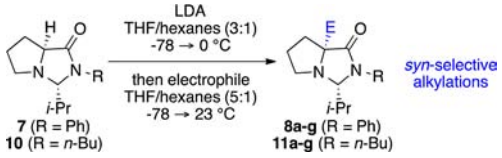
Scheme 1. Alkylation of Isobutyraldehyde-Based Imidazolidinone



We viewed this strategy as a general approach toward this α-quaternary amino amide motif. A number of different alkylating agents were evaluated (Table 1), and we consistently observed formation of the 1,3-*cis* diastereomer. The nature of the amide substituent was inconsequential to the diastereoselectivity, as

Received: November 16, 2013
Published: December 30, 2013

Table 1. *syn*-Selective Alkylations of Isobutyraldehyde-Based Imidazolidinones



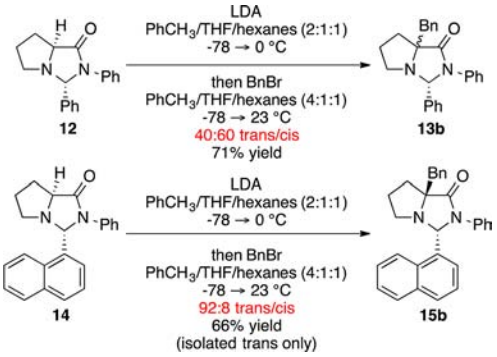
entry	R	electrophile	product	alkylation dr (syn/anti)[a]	yield of cis diast. (%)
1	Ph	MeI	**8a**	>95:5	83
2	*n*-Bu		**11a**	>95:5	73
3	Ph	BnBr	**8b**	>95:5	91
4	*n*-Bu		**11b**	>95:5	85
5	Ph	*n*-BuBr	**8c**	>95:5	77
6	*n*-Bu		**11c**	>95:5	83
7	Ph		**8d**	>95:5	82
8	*n*-Bu		**11d**	>95:5	74
9	Ph		**8e**	>95:5	95
10	*n*-Bu		**11e**	>95:5	62
11	Ph		**8f**	>95:5	76
12	*n*-Bu		**11f**	>95:5	31
13[b]	Ph		**8g**	>95:5	92
14[b]	*n*-Bu		**11g**	>95:5	64

[a]Diastereomeric ratio measured by ^{1}H NMR. [b]LiCl (1.1 equiv) added.

both *N*-phenyl and *N*-*n*-butyl amides displayed high alkylation selectivities.

At this stage, we posed the question whether an *anti*-selective alkylation was possible. Under this premise, an energetically favorable situation must override the aforementioned steric biases that had dictated the *syn*-selective process. Promising results were obtained with benzaldehyde-derived imidazolidinone **12** (Scheme 2). When treated with LDA and BnBr, a

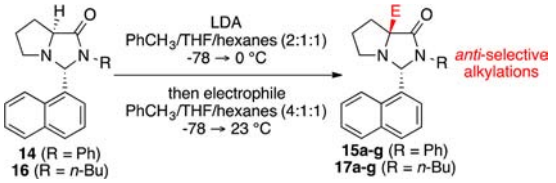
Scheme 2. Alkylations of Aromatic Aldehyde-Based Imidazolidinones



40:60 mixture of *trans* and *cis* diastereomers, respectively, was produced. Following this lead, further investigations ultimately revealed that the 1-naphthaldehyde group highly steered the selectivity toward the *trans* diastereomer (92:8 *trans*/*cis*).[12] Importantly, this outcome is in *substantial contrast* to the isobutyraldehyde-derived imidazolidinone; to our knowledge this example represents the first case of complementary stereoselectivities in the family of SRS reactions based solely on the "temporary" substituent.[13]

We examined the scope of this alkylation and in general obtained high selectivity for the trans diastereomer (Table 2). Only in the case of MeI did we observe substantially compromised diastereoselectivity, yet still favoring formation of the *trans* product. In all cases, the diastereomers were

Table 2. *anti*-Selective Alkylations of 1-Naphthaldehyde-Based Imidazolidinones



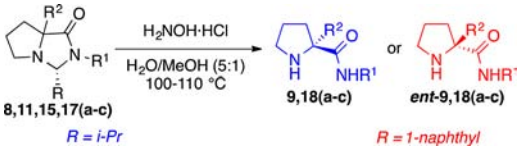
entry	R	electrophile	product	alkylation dr (anti/syn)[a]	yield of trans diast. (%)
1	Ph	MeI	**15a**	68:32	53
2	*n*-Bu		**17a**	91:9	91
3	Ph	BnBr	**15b**	92:8	66
4	*n*-Bu		**17b**	>95:5	90
5	Ph	*n*-BuBr	**15c**	78:22	60
6	*n*-Bu		**17c**	>95:5	99
7	Ph		**15d**	84:16	84
8	*n*-Bu		**17d**	94:6	63
9	Ph		**15e**	74:26	64
10	*n*-Bu		**17e**	>95:5	93
11	Ph		**15f**	91:9	77
12	*n*-Bu		**17f**	92:8	69
13[b]	Ph		**15g**	86:14	77
14[b]	*n*-Bu		**17g**	>95:5	96

[a]Diastereomeric ratio measured by ^{1}H NMR. [b]LiCl (1.1 equiv) added.

chromatographically separable, and the *trans* products were obtained in good overall yields.

Subsequent cleavage of the alkylated aminals would result in a convenient route to enantioenriched α-quaternary amino amide products. Although acid-mediated aminolysis with aniline was effective in some cases (e.g., **8a** → **9a**, Scheme 1), increased steric hindrance rendered this process difficult for others. We hypothesized that using hydroxylamine as the nucleophile would be more successful, due to its enhanced nucleophilicity[14] for intercepting the presumed iminium and the resulting stability of the oxime byproduct.[15,16] Indeed, the target products were accessed via aminolysis in generally excellent yields (Table 3). These overall processes, therefore, represent a divergent strategy toward accessing enantiomeric α-

Table 3. Aminolysis of the Alkylated Imidazolidinones: Stereodivergent α-Quaternary Amino Amide Synthesis



entry	imidazolidinone (R^1,R^2)	amide	yield (%)
1	**8a** (Ph,Me)	**9a**	>99
2	**8b** (Ph,Bn)	**9b**	80
3	**8c** (Ph,*n*-Bu)	**9c**	>99
4	**11a** (*n*-Bu,Me)	**18a**	>99
5[a]	**11b** (*n*-Bu,Bn)	**18b**	70
6[a]	**11c** (*n*-Bu,*n*-Bu)	**18c**	88
7	**15a** (Ph,Me)	***ent*-9a**	>99
8	**15b** (Ph,Bn)	***ent*-9b**	92
9	**15c** (Ph,*n*-Bu)	***ent*-9c**	>99
10	**17a** (*n*-Bu,Me)	***ent*-18a**	98
11	**17b** (*n*-Bu,Bn)	***ent*-18b**	90
12	**17c** (*n*-Bu,*n*-Bu	***ent*-18c**	99

[a]H_2O/1,4-dioxane (3:2) solvent.

dx.doi.org/10.1021/ol403320d | *Org. Lett.* 2014, 16, 432−435

quaternary amino amides and amino acids[17] from the inexpensive, naturally occurring enantiomer of proline.[18]

This stereochemical dichotomy in these alkylations is certainly curious. We believe the isopropyl-based alkylations (Table 1) are aligned with the prior alkylative transformations involving proline-derived *N*,*O*-acetals;[5,19] diastereoselectivity arises primarily from the steric influence of the isopropyl group (Figure 2). In enolate **12**, the all-staggered orientation of the

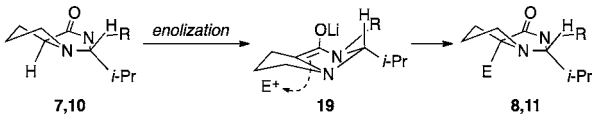


Figure 2. Rationalization for *syn*-selective alkylations.

substituents across the N−C−N bonds positions the pyrrolidine ring above the enolate plane.[20] As the alkylating agent approaches from underneath, the sp^2-hybridized enolate carbon begins to pyramidalize toward forming a *cis*-fused 5,5-ring system. In this reaction trajectory, the *i*-Pr group also moves toward being situated on the convex face of the forming bicycle, avoiding the steric congestion of the concave side.

The effect of the 1-naphthyl group is much more difficult to rationalize. The magnitude and direction of stereoselectivity were relatively consistent for both the *N*-phenyl and *N*-butyl amides, suggesting that arene−arene π interactions are not primary contributors to selection. Figure 3 illustrates our

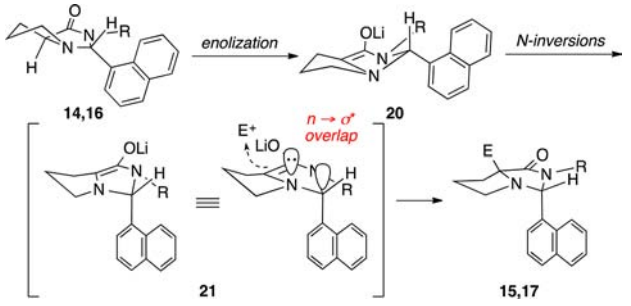


Figure 3. Rationalization for *anti*-selective alkylations.

current hypothesis. Enolization presumably occurs in the same fashion as in the isopropyl system. The *anti* diastereoselectivity suggests that the immediate intermediate enolate must have an inverted central nitrogen atom (i.e., structure **21**). In this orientation, the nitrogen lone pair is located to somewhat delocalize into the C−C σ^* of the aminal-naphthyl bond. Although this positions the naphthyl group on the concave face of the bicyclic enolate, its planarity coupled with its electron-withdrawing nature may sterically and electronically permit this orientation to occur in measurable amounts, in contrast to the isopropyl group.[21,22] This overall rationalization is quite speculative at this stage; both computational and experimental studies are underway to more definitively elucidate the subtle effects of this transformation.

In summary, we have described a remarkable difference in stereoselection in the SRS reaction class. Proline-based aminals can be alkylated with excellent diastereoselectively to form either the *cis* or *trans* diastereomers of α-quaternary analogues, and these products can be subsequently aminolyzed to produce the enantiomeric α-quaternary amino amides. An isopropyl substituent provides a sufficient steric component to lead to *syn* diastereoselectivity. The naphthyl species, in contrast, offers an electronic biasing, which in turn results in *anti* stereoselection. Further investigations into this unique observation of complementary stereoselectivities are ongoing and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectra, and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: emferr@mail.colostate.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Colorado State University and the Donors of the American Chemical Society Petroleum Research Fund are acknowledged for support of this research. Curtis Seizert, Tyler Miller, and Angella Greenawalt are acknowledged for experimental contributions. The Kennan and Rovis groups are acknowledged for sharing HPLC equipment.

■ REFERENCES

(1) Calaza, M. I.; Cativiela, C. *Eur. J. Org. Chem.* **2008**, 3427−3448.

(2) For select recent examples in synthesis and catalysis, see: (a) Frebault, F.; Simpkins, N. S.; Fenwick, A. *J. Am. Chem. Soc.* **2009**, *131*, 4214−4215. (b) Crick, P. J.; Simpkins, N. S.; Highton, A. *Org. Lett.* **2011**, *13*, 6472−6475. (c) Su, B.; Cai, C.; Wang, Q. *J. Org. Chem.* **2012**, *77*, 7981−7987. (d) Tong, S.-T.; Harris, P. W. R.; Barker, D.; Brimble, M. A. *Eur. J. Org. Chem.* **2008**, 164−170.

(3) For select examples in peptidomimetics, see: (a) Genin, M. J.; Johnson, R. L. *J. Am. Chem. Soc.* **1992**, *114*, 8778−8783. (b) Hoffmann, T.; Lanig, H.; Waibel, R.; Gmeiner, P. *Angew. Chem., Int. Ed.* **2001**, *40*, 3361−3364. (c) Vartak, A. P.; Johnson, R. L. *Org. Lett.* **2006**, *8*, 983−986. (d) Bittermann, H.; Böckler, F.; Einsiedel, J.; Gmeiner, P. *Chem.—Eur. J.* **2006**, *12*, 6315−6322.

(4) For a review on SRS, see: Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2708−2748.

(5) For accessing α-quaternary proline-based amino amides using SRS, see: (a) Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390−5398. (b) Beck, A. K.; Blank, S.; Job, K.; Seebach, D.; Sommerfeld, T. *Org. Synth.* **1995**, *72*, 62−73.

(6) (a) Wang, H.; Germanas, J. P. *Synlett* **1999**, 33−36. (b) Artman, G. D., III; Grubbs, A. W.; Williams, R. M. *J. Am. Chem. Soc.* **2007**, *129*, 6336−6342.

(7) Hughes, C. C.; Trauner, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 4556−4559.

(8) Stache, E. E.; Seizert, C. A.; Ferreira, E. M. *Chem. Sci.* **2012**, *3*, 1623−1628.

(9) The stereochemical courses of amide enolate alkylations can often be subject to subtle effects. See: Groaning, M. D.; Meyers, A. I. *Tetrahedron* **2000**, *56*, 9843−9873.

(10) We selected isobutyraldehyde over the traditional pivalaldehyde because of cost and its similar behavior in SRS with amino amides. For a recent example, see: Wang, X.; Xu, Y.; Zhang, L.; Krishnamurthy, D.; Wirth, T.; Nicola, T.; Senanayake, C. H. *Org. Lett.* **2010**, *12*, 4412−4415.

(11) Absolute configuration determined by comparison with an independent synthesis. See the Supporting Information for details.

(12) In these studies we changed the solvent system to a $PhCH_3$/THF/hexanes mixture. We generally observed higher magnitudes of

anti-selectivity with this solvent mixture compared to THF/hexanes, but the directionality was the same in both systems.

(13) There is a lone report of a *syn*-selective alkylation reported based on mandelic acid derivatives: Liu, Y.-Q.; Liu, H.; Zhong, B.; Deng, Y.-L.; Liu, K. *Synth. Commun.* **2005**, *35*, 1403−1412. In this case, the benzaldehyde acetal is illustrated to give the opposite stereochemical outcome than established *anti*-selective results with pivalaldehyde-based acetals.[4] We believe, however, that the configuration of this acetal stereocenter is illustrated incorrectly, and this process is in fact also an *anti*-selective alkylation. Our notion is corroborated by a second report from the same authors, where *anti*-selective alkylations of the benzaldehyde-derived mandelic acid derivative are performed: Han, X.-Y.; Liu, H.; Liu, C.-H.; Wu, B.; Zhong, B.-H.; Liu, K.-L. *J. Chem. Res.* **2004**, 816−817.

(14) For references discussing the α-effect, see: (a) Fina, N. J.; Edwards, J. O. *Int. J. Chem. Kinet.* **1973**, *5*, 1−26. (b) Buncel, E.; Um, I.-K. *Tetrahedron* **2004**, *60*, 7801−7825.

(15) (a) Kalia, J.; Raines, R. T. *Angew. Chem., Int. Ed.* **2008**, *47*, 7523−7526. (b) Wiberg, K. B.; Glaser, R. *J. Am. Chem. Soc.* **1992**, *114*, 841−850.

(16) For a related example of imidazolidinone aminolysis with $H_2NOH{\cdot}HCl$, see: Feenstra, R. W.; Stokkingreef, E. H. M.; Reichwein, A. M.; Lousberg, W. B. H.; Ottenheijm, H. C. J.; Kamphuis, J.; Boesten, W. H. J.; Schoemaker, H. E.; Meijer, E. M. *Tetrahedron* **1990**, *46*, 1745−1756.

(17) Related imidazolidinone hydrolysis to amino acid: Seebach, D.; Dziadulewicz, E.; Behrendt, L.; Cantoreggi, S.; Fitzi, R. *Liebigs Ann. Chem.* **1989**, 1215−1232.

(18) In the naphthyl systems, we have eliminated the possibility of an *endo*-selective condensation with subsequent *syn*-selective alkylation and aminolysis. See the Supporting Information for details.

(19) No "memory effect" was observed in the process, evaluated by alkylation of a formaldehyde-derived imidazolidinone. See Supporting Information.

(20) Pyramidalization of both nitrogens of the imidazolidinone should occur upon enolization. This orientation is aligned with a proposed transition state in the alkylations of imidazolidinones based on glycine derivatives. See: Seebach, D.; Juaristi, E.; Miller, D. D.; Schickli, C.; Weber, T. *Helv. Chim. Acta* **1987**, *70*, 237−261.

(21) The hypothesis is also consistent with the 1-naphthyl group being more electron-withdrawing than a phenyl ring, aligned with the stereoselectivity trend in Scheme 2.

(22) Interestingly, the 1-naphthyl group behaves similarly to the *tert*-butyl group in mandelic acid derivative alkylations. See: Misaki, T.; Ureshino, S.; Nagase, R.; Oguni, Y.; Tanabe, Y. *Org. Process Res. Dev.* **2006**, *10*, 500−504.