HHS Public Access

Author manuscript

J Am Chem Soc. Author manuscript; available in PMC 2016 May 13.

Published in final edited form as:

J Am Chem Soc. 2015 May 13; 137(18): 5871–5874. doi:10.1021/jacs.5b02065.

γ, δ, ε-C(sp³)–H Functionalization through A Directed Radical H-Abstraction

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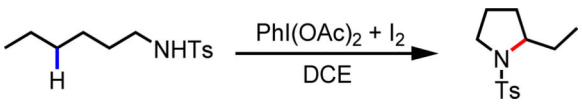
Abstract

Aliphatic amides are selectively functionalized at the γ and δ–positions through a directed radical 1,5 and 1,6-H-abstraction. The initially formed γ- or δ-lactams are intercepted by NIS and $TMSN_3$ leading to multiple C–H functionalizations at the γ, δ, and ε–positions. This new reactivity is exploited to convert alkyls into amino alcohols or allylic amines.

Pd-catalyzed β-C–H functionalizations of aliphatic acids using directing groups have been extensively studied in the past decade. A diverse range of transformations have been developed using both Pd(II)[1], Pd(0)[2] and other transition metal catalysts.[3] In contrast, γ-C–H functionalizations are still rare.[4] Inspired by pioneering studies on 1,5 and 1,6-H-abstraction,[5, 6] we questioned whether the reactivity and selectivity of these radical abstraction could be harnessed to develop wide range of catalytic C–H functionalization reactions of aliphatic acids or amides. An extensive literature survey revealed two potential challenges. First, radical abstractions of γ- or δ-C–H bonds of aliphatic amides have only been demonstrated for C–H bond adjacent to an oxygen atom.[6d] Second, the vast majority of the reactions initiated by nitrogen radicals leads to cyclization (eq 1)[6e] instead of intermolecular functionalizations with the exception of a few examples involving amine substrates.[6c] This suggests that the facile cyclization pathway might be difficult to prevent. Herein we report an empirically discovered a sequential radical γ-, or δ-C–H lactamization and subsequent reaction with NIS and $TMSN_3$ to give δ-iodo-γ-lactams or δ, ε-dehydrogenated γ-lactams. Structural elaborations of these highly functionalized lactams allows for an overall conversion of simple alkyls into olefins, amino alcohols or allylic amines.



(1)

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Supporting Information Available: Experimental procedures and spectral data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

Our initial efforts to trigger the radical H-abstraction by the amide were guided by the conditions used for radical cyclization of toluenesulfonyl protected amines.[6e] We choose to use our *N*-heptafluorotolyl amide (**PG^1**) directing group[1b] anticipating this would accommodate subsequent functionalizations with a metal catalyst if the γ-carbon centered radical is formed and intercepted by the metal. Through an extensive survey of radical initiators, iodine sources, solvents and other parameters (see Supporting Information for details), it was found that a combination of $PhI(OAc)_2$ and I_2 facilitated the desired lactamization reaction of **1a** to give the γ-lactamization product **2a** in excellent yield (Scheme 1A). Next, we sought to identify an appropriate metal catalyst or reagent that can intercept the γ-carbon centered radical prior to the cyclization thereby achieving a general intermolecular γ-C–H functionalization method.

While all efforts to trap the γ-carbon centered radical with various Cu, Pd and Ni catalysts were not fruitful, the attempt to perform a radical γ-azidation led to a surprising finding. In the presence of $TMSN_3$, the reaction of **1a** with NIS in DCE afforded δ-iodo γ-lactam **3a** in which both γ- and δ-C–H bonds are functionalized (Scheme 1, B). This reactivity was further investigated with a range of amide directing groups. While *N*-methoxy and *N*-alkyl amides did not give rise to any product, *N*-phenyl and *N*-sulfonyl amides are generally reactive (Table 1). The highly acidic *N*-heptafluorotolyl (**PG^1**) and the *N*-para-trifluoromethyl phenylsulfonyl (**PG^2**) amides are more effective affording the δ-iodo γ-lactams in 86% and 72% yields respectively (Table 1).

Monitoring the reaction by ^{1}H NMR and isolation of γ-lactam **2c** by shortening the reaction to 2 h suggests that **2c** is initially formed as the intermediate which then reacts with $TMSN_3$ and NIS to give iodo lactam **3c** (Scheme 2, A). Apparently, the *in situ* generated azide radical[7] triggers a β-C–N bond scission to give the terminal double bond and subsequent iodolactamization affords **3c**. The iodolactamization step is verified by subjecting a synthetic standard **4b** to the reaction conditions to give **3c**. Importantly, the iodo lactam **3a** and **3b** can be converted to γ, δ-desaturated amide **4a** and **4b** respectively, thus leading to a method for dehydrogenation (Scheme 3).[8, 9] In addition, the iodo lactam **3c** protected with *para*-trifluoromethyl phenylsulfonyl group (**PG^2**) is subjected to methanolysis conditions to give **5** containing a synthetically useful 1,2-amino alcohol motif.

The smooth conversion of the iodo lactam products to more useful olefin and 1,2-amino alcohol motifs prompted us to examine the scope of this transformation. Substrate **1d** containing both a methyl and ethyl group at the γ-position was subjected to the reaction conditions. While the first lactamization event is expected to occur selectively at the tertiary carbon center, the subsequent H-abstraction by the azide radical at the δ-carbon center could occur at either methyl or the ethyl group leading to different products. The exclusive formation of **3d** (Table 2) containing the newly installed iodide on the methylene carbon suggests that the radical abstraction by the azide radical occurs selectively at the methylene carbon (Scheme 2, B). Similarly, product **3e** was obtained with substrate **1e**. This method also allows access to synthetically useful iodinated spiro lactams **3g** and **3h** from **1g** and **1h** respectively.

For substrates containing substituents at the α and β positions, low yields (~40%) were obtained when the *para*-trifluoromethyl phenylsulfonyl (**PG**^{2}) protecting group was used. Thus, **1i–1l** containing *N*-heptafluorotolyl (**PG**^{1}) protecting groups were prepared for testing. We found that the desired bicyclic δ iodo lactam (**3i**) was formed in 72% yield. Other amides containing methyl, acetoxy and tetrachlorophthalimide at α or β carbons are all compatible, giving the desired products in good yields (**3j–3l**). Notably, **3l** can be converted to γ, δ-unsaturated chiral amino acid, providing a new method to functionalize leucine. Since previous protocols for functionalizing leucine via radical H-abstraction are directed by the amino group,[6c, 8] the use of this amide as a directing group in reaction provides a complimentary method to dehydrogenate leucine.

To investigate whether this protocol can be extended to the functionalizations of δ, ε-C–H bonds, we prepared amide substrates **6a–6d** containing tertiary C–H bonds at the δ position (Table 3). Interestingly, **6a** was converted to δ, ε-dehydrogenated γ-lactam **7a** under the standard conditions. Apparently, the olefin intermediate bearing a radical on the nitrogen center derived from the initially formed δ-lactam underwent the facile intramolecular radical abstraction at the allylic carbon center, leading to the cyclization product **7a** (Scheme 4). The ε-methylene C–H bond in **6b** is selectively functionalized in the presence of the ε-methyl C–H bond. Cyclopentyl (**6c**) and cyclohexyl (**6d**) are also compatible, albeit affording lower yields. A minor product derived from the radical abstraction of the ε-methyl C–H bond was also obtained with the cyclic substrate **7d**. Importantly, these lactam products can be readily converted to synthetically useful δ, ε-desaturated γ-aminoesters as shown in Scheme 5. For example, **7a** is converted to **8**, a compound that is closely related to Vigabatrin.

In conclusion, we have developed a protocol to functionalize γ, δ, ε-C–H bonds of aliphatic acids via a radical 1,5 and 1,6-H-abstraction. The terminal alkyl groups of aliphatic amides are converted to olefins, amino alcohols or allylic amines.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

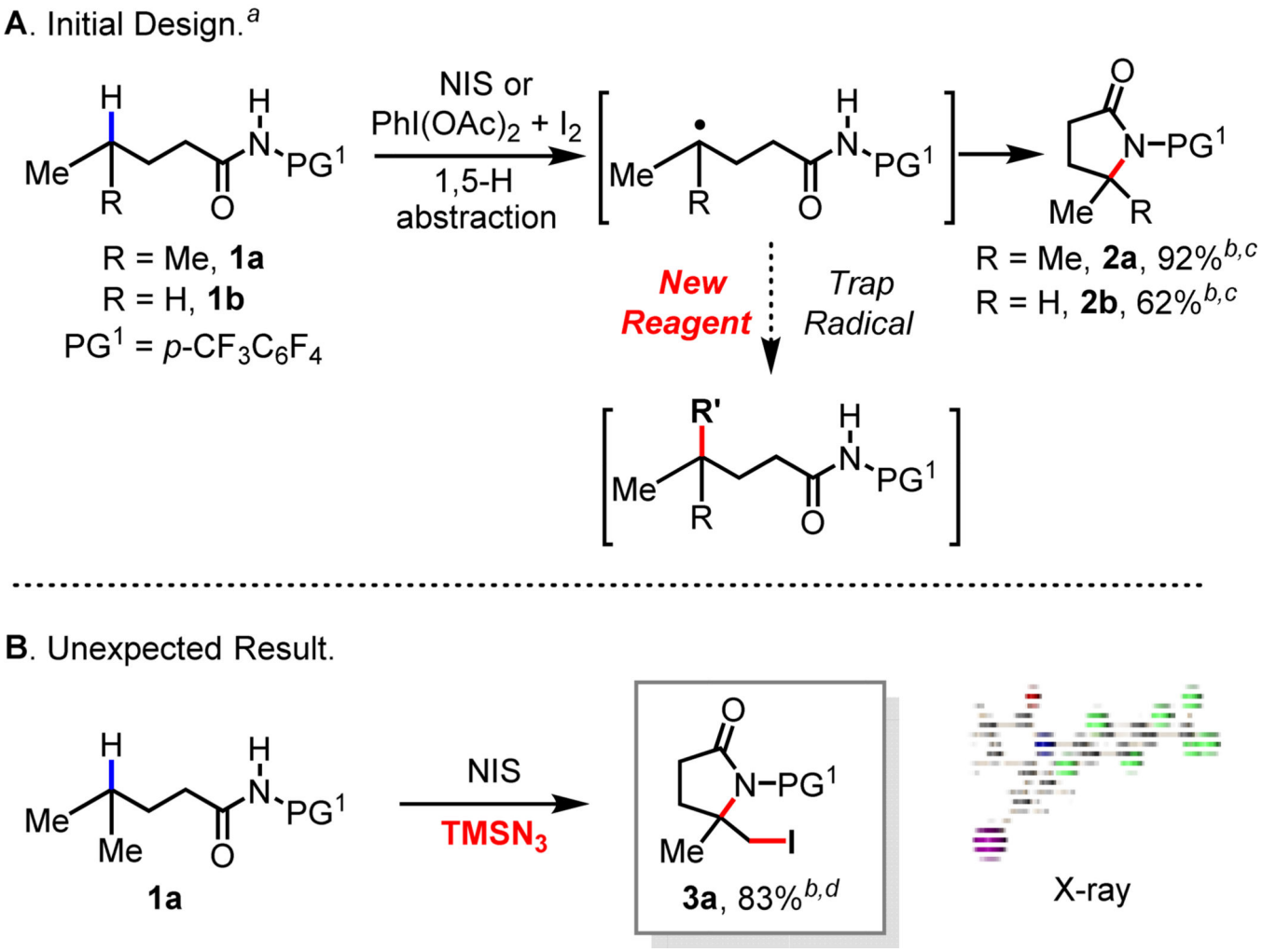
We gratefully acknowledge The Scripps Research Institute and the NIH (NIGMS, 2R01GM084019) for financial support.

References

1. For selected examples: Wang D-H, Wasa M, Giri R, Yu J-Q. J. Am. Chem. Soc. 2008; 130:7190. [PubMed: 18479089] Wasa M, Engle KM, Yu J-Q. J. Am. Chem. Soc. 2010; 132:3680. [PubMed: 20187642] Shabashov D, Daugulis O. J. Am. Chem. Soc. 2010; 132:3965. [PubMed: 20175511] Zhang S-Y, Li Q, He G, Nack WA, Chen G. J. Am. Chem. Soc. 2013; 135:12135. [PubMed: 23919290] He G, Zhang S-Y, Nack WA, Li Q, Chen G. Angew. Chem. Int. Ed. 2013; 52:11124. Nadres ET, Santos GIF, Shabashov D, Daugulis O. J. Org. Chem. 2013; 78:9689. [PubMed: 24090404] Chen K, Hu F, Zhang S-Q, Shi B-F. Chem. Sci. 2013; 4:3906. He J, Li S-H, Deng Y-Q, Fu H-Y, Laforteza BN, Spangler JE, Homs A, Yu J-Q. Science. 2014; 343:1216. [PubMed: 24626923] Zhu R-Y, He J, Yu J-Q. J. Am. Chem. Soc. 2014; 136:13194. [PubMed: 25208210]

Xiao K-J, Lin DW, Miura M, Zhu R-Y, Gong W, Wasa M, Yu J-Q. J. Am. Chem. Soc. 2014; 136:8138. [PubMed: 24815880]

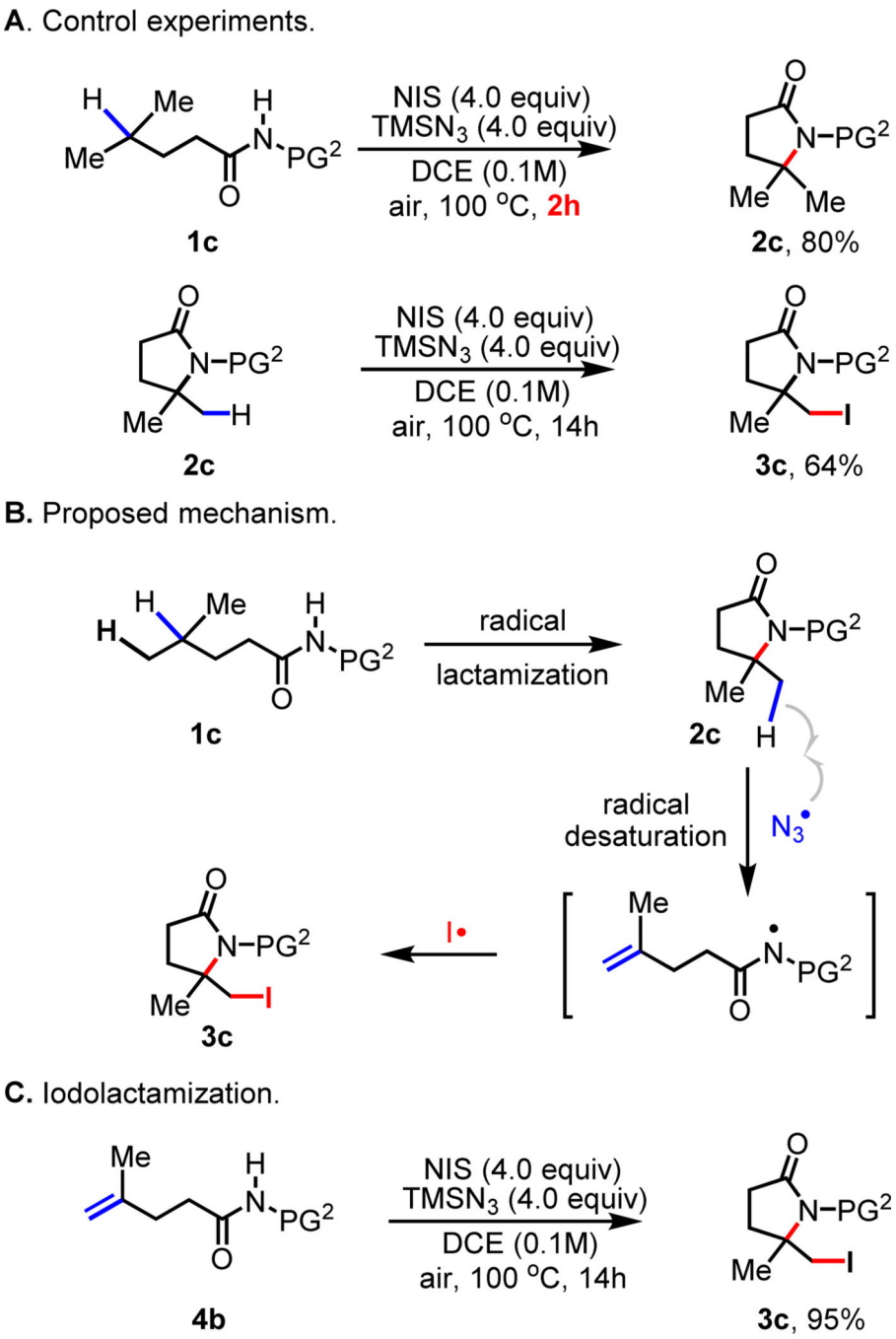
2. (a) Wasa M, Engle KM, Yu J-Q. J. Am. Chem. Soc. 2009; 131:9886. [PubMed: 19580277] (b) He J, Wasa M, Chan K, Yu J-Q. J. Am. Chem. Soc. 2013; 135:3387. [PubMed: 23406445]
3. For selected examples: Shang R, Ilies L, Matsumoto A, Nakamura E. J. Am. Chem. Soc. 2013; 135:603. Aihara Y, Chatani N. J. Am. Chem. Soc. 2014; 136:898. [PubMed: 24377655] Wang Z, Ni J, Kuninobu Y, Kanai M. Angew. Chem. Int. Ed. 2014; 53:3496. Wu X, Zhao Y, Ge H. Chem. Asian J. 2014; 9:2736. [PubMed: 25059113]
4. (a) He G, Zhang S-Y, Nack WA, Li Q, Chen G. Angew. Chem. Int. Ed. 2013; 52:11124.(b) Li S-H, Chen G, Feng C-G, Gong W, Yu J-Q. J. Am. Chem. Soc. 2014; 136:5267. [PubMed: 24666182]
5. Selected examples of 1,5 and 1,6-H-abstraction initiated by an oxygen radical: Barton DHR, Beaton JM, Geller LE, Pechet MM. J. Am. Chem. Soc. 1960; 82:2640. Barton DHR, Beaton JM, Geller LE, Pechet MM. J. Am. Chem. Soc. 1961; 83:4076. Mihailovic ML, Miloradovic M. Tetrahedron. 1966; 22:723. Concepcion JI, Francisco CG, Hernandez R, Salazar JA, Suarez E. Tetrahendron Lett. 1984; 25:1953. Francisco CG, Herrera AJ, Suarez E. J. Org. Chem. 2002; 67:7439. [PubMed: 12375977] Zhu H, Wickenden JG, Campbell NE, Leung JCT, Johnson KM, Sammis GM. Org. Lett. 2009; 11:2019. [PubMed: 19326922] Kundu R, Ball ZT. Org. Lett. 2010; 12:2460. [PubMed: 20438056]
6. Selected examples of 1,5 and 1,6-H-abstraction initiated by a nitrogen radical: Corey EJ, Hertler WR. J. Am. Chem. Soc. 1960; 82:1657. Togo H, Hoshina Y, Muraki T, Nakayama H, Yokoyama M. J. Org. Chem. 1998; 63:5193. Reddy LR, Reddy BVS, Corey EJ. Org. Lett. 2006; 8:2819. [PubMed: 16774265] Francisco CG, Herrera AJ, Martin A, Perez-Martin I, Suarez E. Tetrahedron Lett. 2007; 48:6384. Fan R, Pu D, Wen F, Wu J. J. Org. Chem. 2007; 72:8994. [PubMed: 17929871] Chen K, Richter JM, Baran PS. J. Am. Chem. Soc. 2008; 130:7247. [PubMed: 18481847]
7. (a) Magnus P, Lacour J. J. Am. Chem. Soc. 1992; 114:767.(b) Marinescu LG, Pedersen CM, Bols M. Tetrahedron. 2005; 61:123.(c) Pedersen CM, Marinescu LG, Bols M. Org. Biomol. Chem. 2005; 3:816. [PubMed: 15731868] (d) Chouthaiwale PV, Suryavanshi G, Sudalai A. Tetrahedron Lett. 2008; 49:6401.
8. Voica AF, Mendoza A, Gutekunst WR, Fraga JO, Baran PS. Nat. Chem. 2012; 4:629. [PubMed: 22824894]
9. Giri R, Maugel NL, Foxman BM, Yu J-Q. Organometallics. 2008; 27:1667.



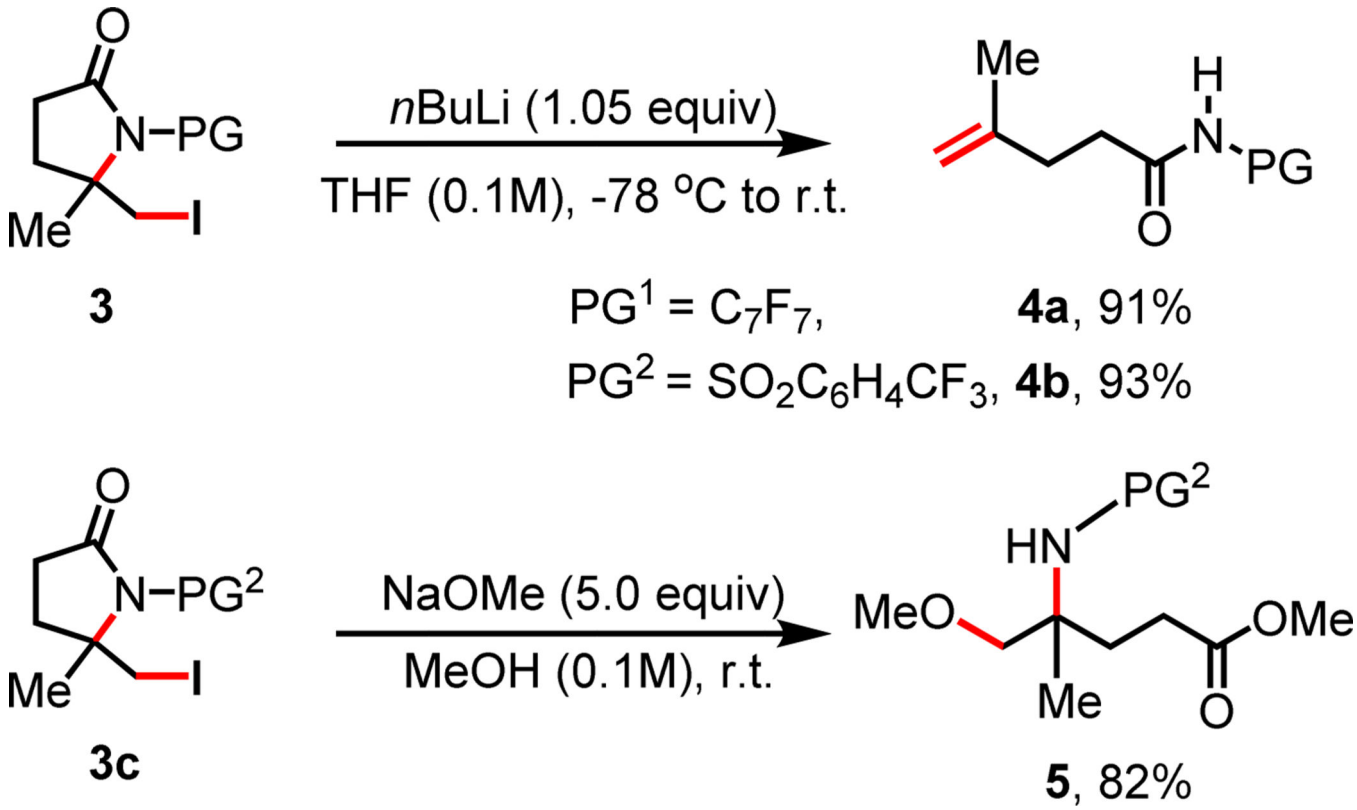
Scheme 1.

Initial Design and Unexpected Results

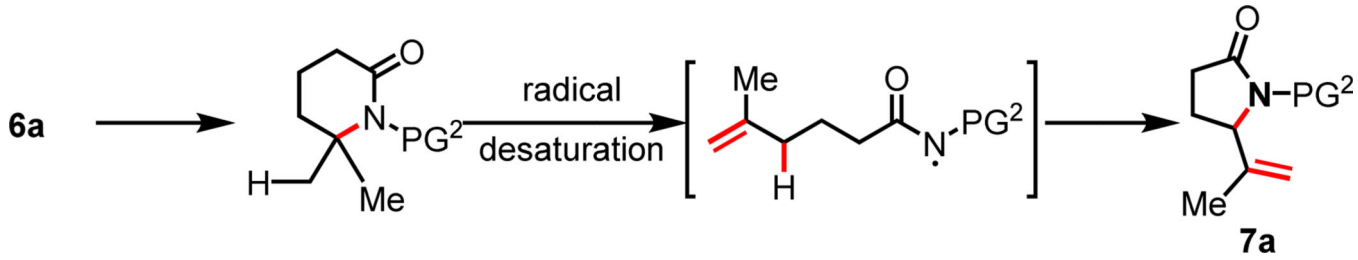
[a]Condition A: **1a** (0.1 mmol), NIS (3 equiv.), DCE (1 mL), 100 °C, air, 14 h. Condition B: **1a** (0.1 mmol), $PhI(OAc)_2$ (1.5 equiv.), I_2 (1.5 equiv.), DCE, r.t., air, 48 h. [b]Isolated yield. [c]For substrate **1a**, isolated yield of **2a** is 92% (condition A) and 89% (condition B); for substrate **1b**, isolated yield of **2b** is 62% (condition A). [d]Product structure is confirmed by X-ray crystallographic analysis.



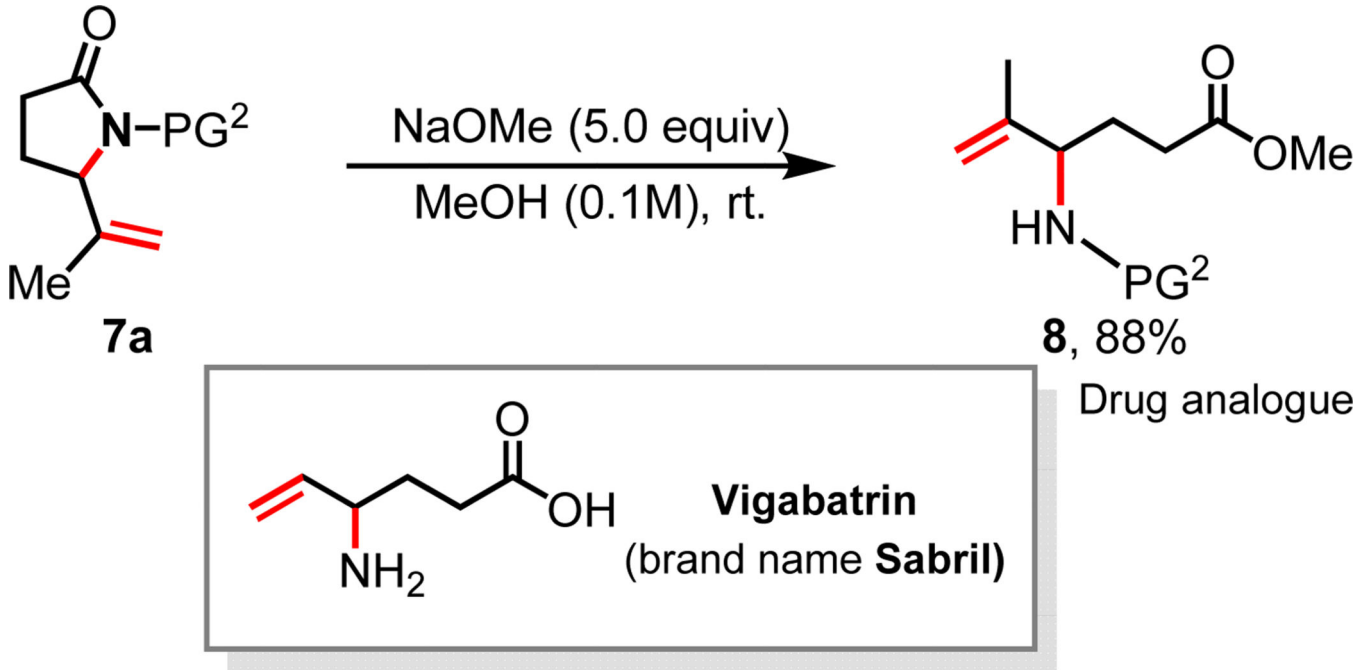
Scheme 2.
Preliminary Mechanistic Investigations



Scheme 3.
Synthetic application of δ-iodo γ-lactam 3



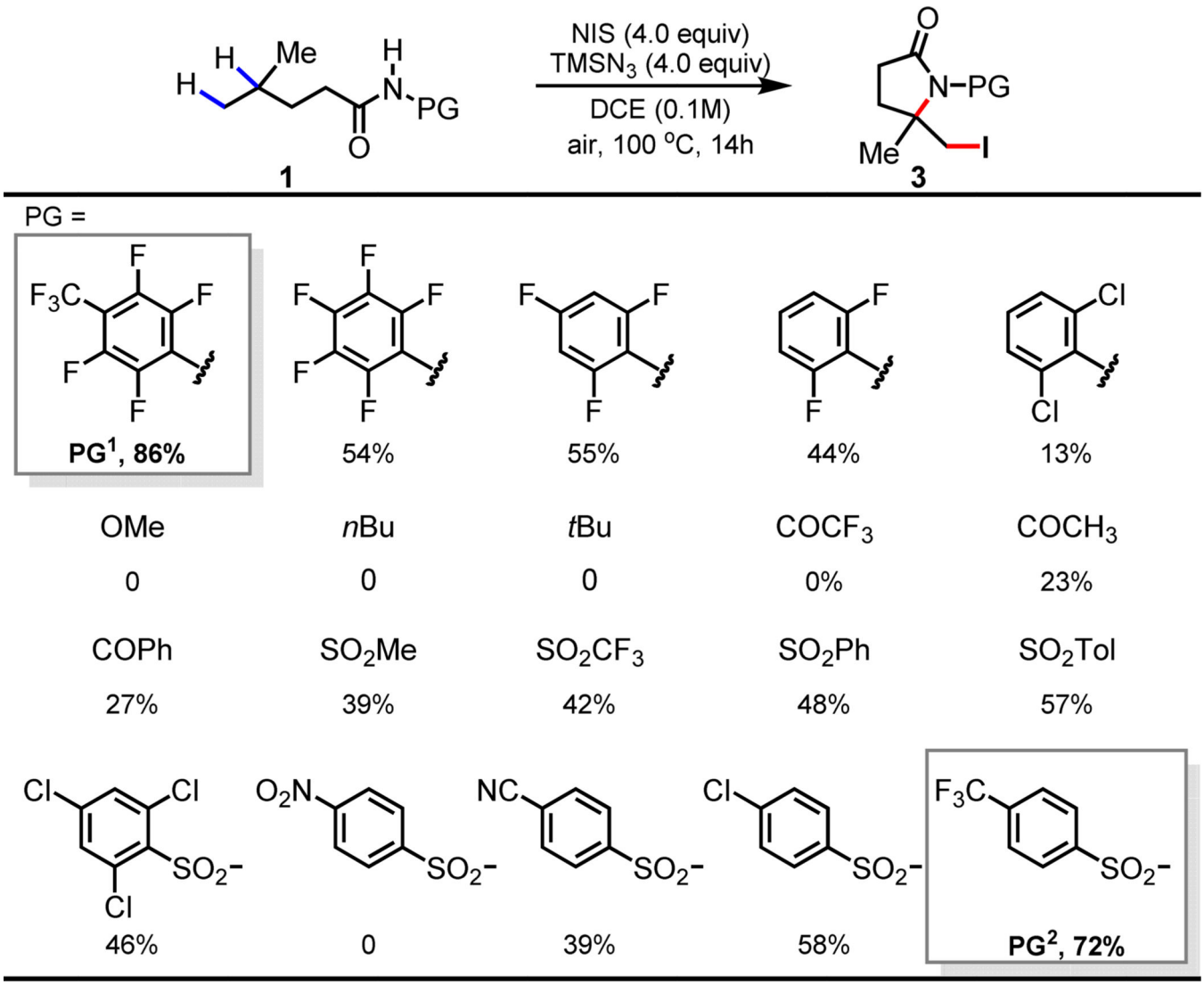
Scheme 4.
Proposed Mechanism for the Formation of δ, ε Vinyl Lactams



Scheme 5.
Synthetic Application of δ, ε Vinyl Lactams

Table 1

Protecting Group Screening[a,b]

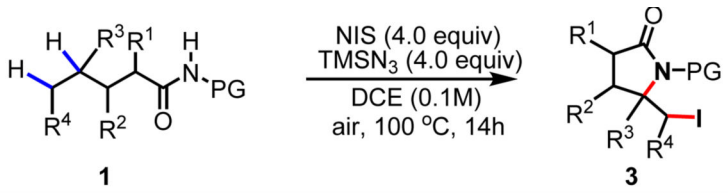


[a] Conditions: **1** (0.1 mmol), NIS (4 equiv.), $TMSN_3$ (4 equiv.), DCE (1 mL), 100 °C, air, 14 h.

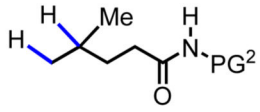
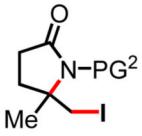
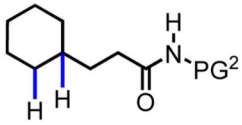
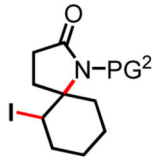
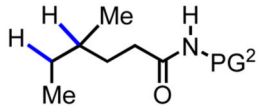
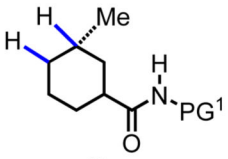
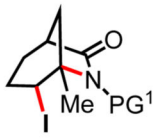
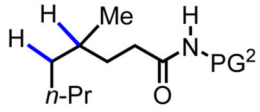
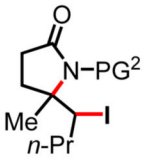
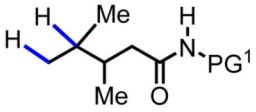
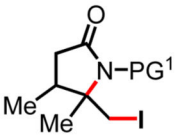
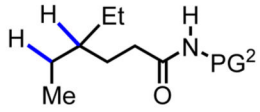
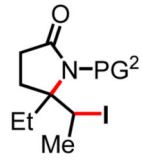
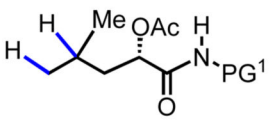
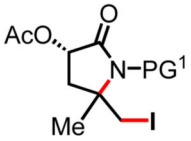
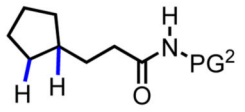
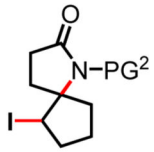
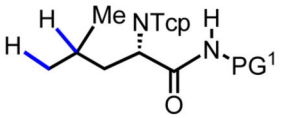
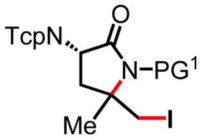
[b] Yields were determined by ^1H NMR analysis of the crude reaction mixture using CH_2Br_2 as an internal standard.

Table 2

γ, δ–Iodolactamization of Aliphatic Amides[a,b]



1 3

Substrate	Product	Substrate	Product
 **1c**	 **3c**, 72%, 53%[c]	 **1h**	 **3h**, 70%
 **1d**	 **3d**, 71%[d]	 **1i**	 **3i**, 72%
 **1e**	 **3e**, 53%[d]	 **1j**	 **3j**, 61%[d]
 **1f**	 **3f**, 63%	 **1k**	 **3k**, 62%[d]
 **1g**	 **3g**, 48%	 **1l**	 **3l**, 72%[d,e]

[a] Conditions: **1** (0.1 mmol), NIS (4 equiv.), $TMSN_3$ (4 equiv.), DCE (1 mL), 100 °C, air, 14 h.

[b] Isolated yields.

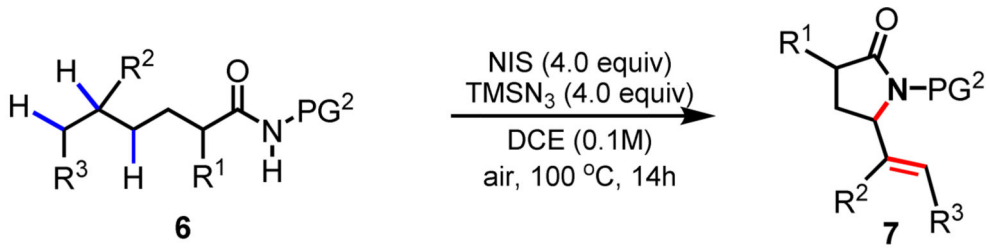
[c] Run on gram-scale.

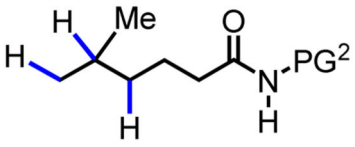
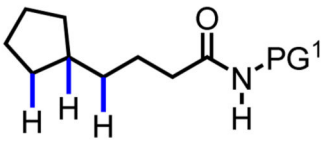
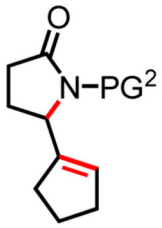
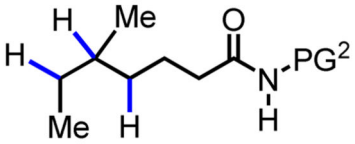
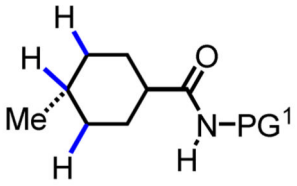
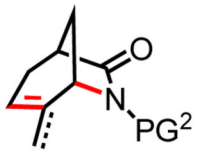
[d] Obtained as a mixture of diastereomers (See Supporting Information).

[e] Tcp = tetrachlorophthalimide. One pot procedure for substrate **1l**: NIS (2 equiv.), 100 °C, air, 8h; I_2 (3 equiv.) and $TMSN_3$ (4 equiv.), 100 °C, 14h.

Table 3

γ, δ, ε–C–H Functionalizations of Aliphatic Amides[a,b]



Substrate	Product	Substrate	Product
 **6a**	 **7a**, 71%	 **6c**	 **7c**, 44%
 **6b**	 **7b**, 58%	 **6d**	 **7d**, 54%[c]

[a] Conditions: **6** (0.1 mmol), NIS (4 equiv.), TMSN3 (4 equiv.), DCE (1 mL), 100 °C, air, 14 h.

[b] Isolated yields.

[c] Obtained as a mixture of inseparable mixture of diastereomers (methylene:methyl = 3:1).