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γ,δ,ε-C(sp^3)–H Functionalization through Directed Radical H-Abstraction

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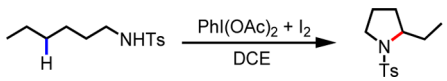
Supporting Information

ABSTRACT: Aliphatic amides are selectively functionalized at the γ- and δ-positions through directed radical 1,5 and 1,6 H-abstractions, respectively. The initially formed γ- or δ-lactams are intercepted by *N*-iodosuccinimide and trimethylsilyl azide, leading to double and triple C–H functionalizations at the γ-, δ-, and ε-positions. This new reactivity is exploited to convert alkyls into amino alcohols and 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 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-abstractions,[5,6] we questioned whether the reactivity and selectivity of these radical abstractions could be harnessed to develop a 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 been demonstrated only for C–H bonds adjacent to an oxygen atom.[6d] Second, the vast majority of the reactions initiated by nitrogen radicals lead to cyclization (eq 1)[6e] instead of intermolecular functionalizations, with the

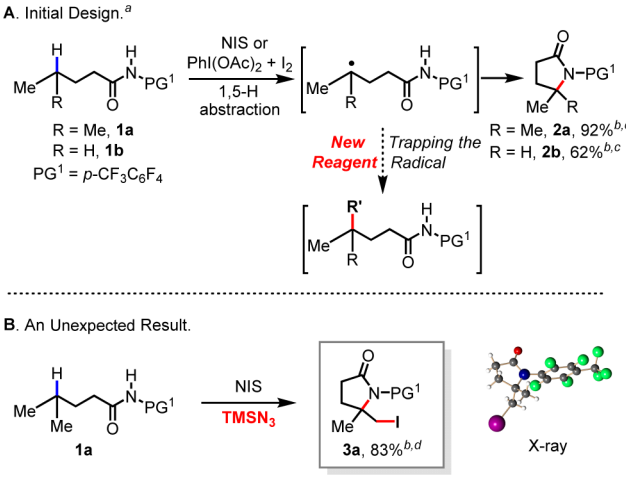


(1)

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 *N*-iodosuccinimide (NIS) and trimethylsilyl azide ($TMSN_3$) to give δ-iodo-γ-lactams or δ,ε-dehydrogenated γ-lactams. Structural elaborations of these highly functionalized lactams allow the overall conversion of simple alkyls into difunctionalized olefins, amino alcohols, or trifunctionalized allylic amines.

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 chose to use our *N*-heptafluorotolylamide directing group (PG^1),[1b] anticipating that 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 the Supporting Information for details), it was found that a combination of $PhI(OAc)_2$ and I_2 facilitates the desired lactamization reaction of **1a** to give the γ-lactamization product **2a** in excellent yield (Scheme 1A). Next,

Scheme 1. Initial Design and an Unexpected Result



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

we sought to identify an appropriate metal catalyst or reagent that could 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 were functionalized (Scheme 1B). This reactivity was further investigated with a range of amide directing groups. While *N*-methoxy- and *N*-alkylamides did not give rise to any product, *N*-phenyl- and *N*-sulfonylamides were generally reactive (Table 1). The highly acidic *N*-heptafluorotolylamide (PG^1) and *N*-*p*-trifluoromethylphenylsulfonylamide (PG^2) were more effective,

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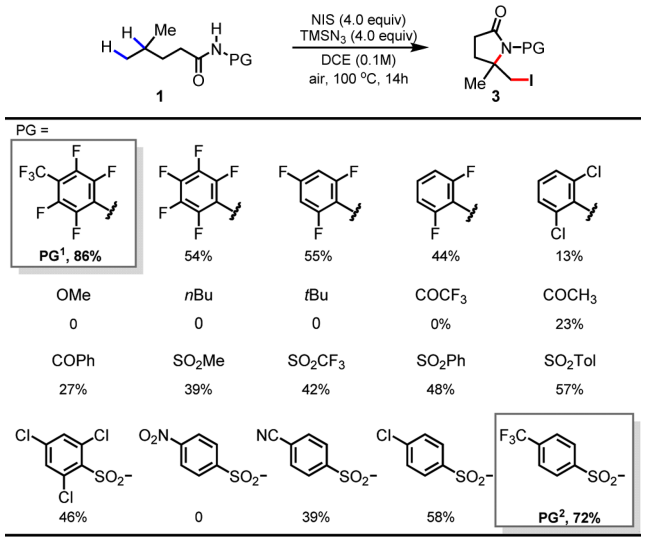
Table 1. Screening of Protecting Groups[a,b]

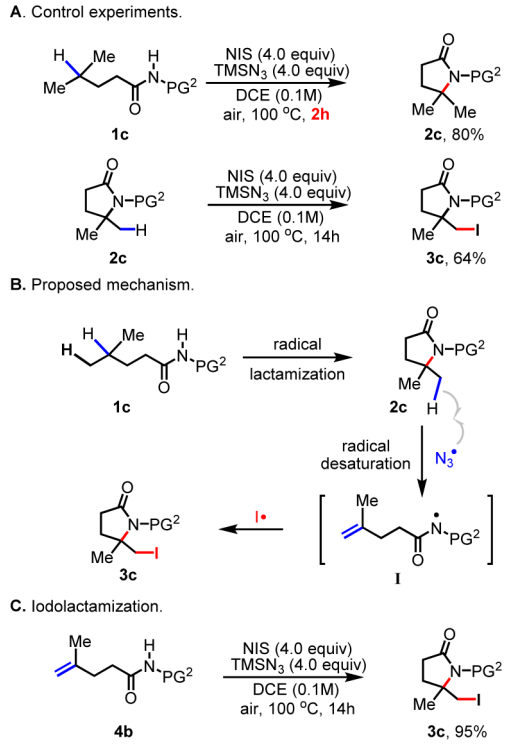


[a]Conditions: **1** (0.1 mmol), NIS (4 equiv), $TMSN_3$ (4 equiv), DCE (1 mL), 100 °C, air, 14 h. [b]Yields were determined by ^1H NMR analysis of the crude reaction mixtures using CH_2Br_2 as an internal standard.

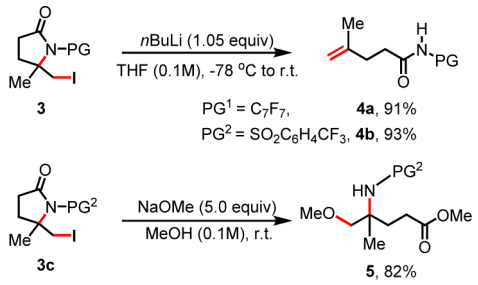
affording the δ-iodo-γ-lactams in 86% and 72% yield, respectively (Table 1).

Monitoring of the reaction by ^1H NMR spectroscopy and isolation of γ-lactam **2c** by shortening the reaction time to 2 h suggested that **2c** is initially formed as an intermediate and then reacts with $TMSN_3$ and NIS to give iodolactam **3c** (Scheme 2A). Apparently, the in situ-generated azide radical[7] triggers β-C−N bond scission to give the terminal double bond, and subsequent radical cyclization affords **3c** (Scheme 2B). Alternatively, the radical intermediate **I** could abstract a hydrogen from **2c** to initiate a radical chain reaction to produce **4b**, which would undergo standard iodolactamization[8] to give **3c**. The iodolactamization step was verified by subjecting a synthetic standard **4b** to the typical reaction conditions to give **3c** (Scheme 2, C). Importantly, iodolactams **3a** and **3b** can be converted to γ,δ-desaturated amides **4a** and **4b**, respectively, thus leading to a method for dehydrogenation (Scheme 3).[9,10] In addition, iodolactam **3c** protected with the

Scheme 2. Preliminary Mechanistic Investigations



Scheme 3. Synthetic Applications of δ-Iodo-γ-lactams 3



p-trifluoromethylphenylsulfonyl group ($\mathbf{PG^2}$) was subjected to methanolysis conditions to give **5** containing a synthetically useful 1,2-amino alcohol motif.

The smooth conversion of the iodolactam 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 group and an ethyl group at the γ-position was subjected to the reaction conditions. While the first lactamization event was 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 the methyl or ethyl group, leading to different products. The exclusive formation of **3d** containing the newly installed iodo group on the methylene carbon (Table 2) suggests that the radical abstraction by the azide radical occurs selectively at the methylene carbon (Scheme 2B). Similarly, product **3e** was obtained with substrate **1e**. This method also allows access to synthetically useful iodinated spirolactams **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 *p*-trifluoromethylphenylsulfonyl protecting group ($\mathbf{PG^2}$) was used. Thus, **1i**−**l** containing the *N*-heptafluorotolyl protecting group ($\mathbf{PG^1}$) were prepared for testing. We found that the desired bicyclic δ-iodolactam **3i** was formed from **1i** in 72% yield. Other amides containing methyl, acetoxy, and tetrachlorophthalimide at the α- or β-carbon were all compatible, giving the desired products (**3j**−**l**) in good yields. Notably, **3l** can be converted to a γ,δ-unsaturated chiral amino acid, providing a new method to functionalize leucine. Since previous protocols for functionalization of leucine via radical H-abstraction are directed by the amino group,[6c,9] the use of this amide as a directing group in the reaction provides a complementary method for dehydrogenation of leucine.

To investigate whether this protocol can be extended to the functionalizations of δ- and ε-C−H bonds, we prepared amide substrates **6a**−**d** 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

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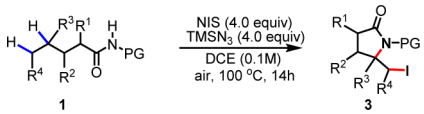
Table 2. δ-Iodo-γ-lactamization of Aliphatic Amides[a,b]

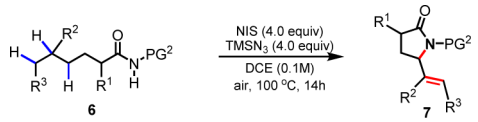


1 3

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

[a]Conditions: **1** (0.1 mmol), NIS (4 equiv), $TMSN_3$ (4 equiv), DCE (1 mL), 100 °C, air, 14 h. [b]Isolated yields are shown. [c]Run on a gram scale. [d]Obtained as a mixture of diastereomers (3:2). [e]Obtained as a mixture of diastereomers (7:6). [f]Obtained as a mixture of diastereomers (2:1). [g]Tcp = tetrachlorophthalimide. One-pot procedure for substrate **1l**: NIS (2 equiv), 100 °C, air, 8 h; I_2 (3 equiv), $TMSN_3$ (4 equiv), 100 °C, 14 h.

Table 3. γ,δ,ε-C−H Functionalizations of Aliphatic Amides[a,b]



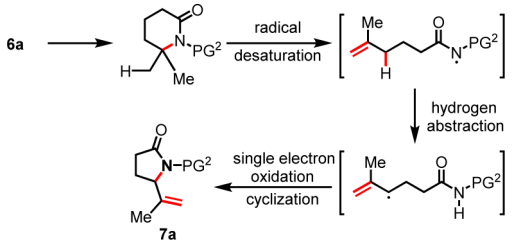
6 7

Substrate	Product	Substrate	Product
6a	7a, 71%, X-ray[c]	6c	7c, 44%
6b	7b, 58%[d]	6d	7d, 54%[e]

[a]Conditions: **6** (0.1 mmol), NIS (4 equiv), $TMSN_3$ (4 equiv), DCE (1 mL), 100 °C, air, 14 h. [b]Isolated yields are shown. [c]The structure of **7a** was confirmed by X-ray crystallographic analysis. [d]Obtained as a mixture of isomers (5:1). [e]Obtained as a mixture of isomers (3:1).

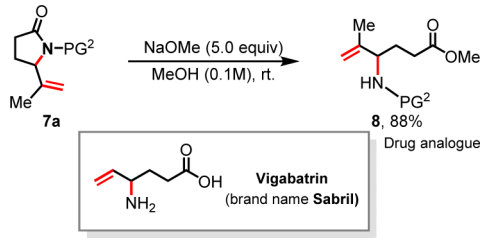
allylic carbon center, leading to the cyclization product **7a** (Scheme 4). The initial formation of the δ-lactam instead of the γ-lactam can be attributed to the higher reactivity of the tertiary

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



C−H bonds at the δ-position. 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**) groups 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-amino esters, as shown in Scheme 5. For example, **7a** can be converted to **8**, a compound that is closely related to vigabatrin.

Scheme 5. Synthetic Application of δ,ε-Vinyl Lactams



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

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b02065.

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Notes

The authors declare no competing financial interest.

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