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COMMUNICATION

Trans-selective cyclizations of alpha-bromocarboxamides and E/Z-mixed internal olefins catalyzed by a Fe salt

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There are several reports of lactam cyclizations, but most yield less-substituted lactam rings. Therefore, diastereoselective cyclization to yield highly substituted lactams is one of the challenges in this field. We therefore propose a strategy involving the reactions of α-halocarboxamides with *E*/*Z*-mixed internal olefins here. An Fe/triphos catalyst system is effective in reactions between α-bromocarboxamides and internal olefins to form *trans* lactams with quaternary carbons. Control experiments reveal that the reaction involves a radical process. This reaction may be useful in the field of pharmaceuticals, as γ-lactam moieties constitute the core structures of numerous drugs and natural alkaloids.

γ-Lactam moieties are some of the most critical heterocyclic motifs that constitute the core structures of numerous natural alkaloids, drugs, and bioactive natural and non-natural molecules[1]. Although there are numerous approaches in synthesizing γ-lactams[2], the diastereoselective preparation of highly substituted, complex γ-lactams remains challenging. Recent progress in this area includes: 1) a transition-metal-catalyzed C–H alkylation using a terminal olefin reported by Yu[3], Li[4], Li, and Wang[5] (Figure 1a). 2) Radical cyclization of an α-halocarboxamide and a terminal olefin in the presence of a radical initiator reported by Hull et al.[6], Tang, Wang et al.[7], and our group[8] (Figure 1b). Most reports of intermolecular γ-lactamizations employ terminal olefins, and reactions with internal olefins are unsuitable because of their low reactivities. Onitsuka et al. resolved this serious reactivity problem using a unique methodology[9]. They used an (*E*)-allylic halide as an internal olefin, with asymmetric γ-lactamizations occurring via allylation (Figure 1c). However, stereoconvergent γ-lactamizations using *E*/*Z*-mixed internal olefins are very attractive because the syntheses of sterically pure internal olefins are not simple.

Previously, our group reported Fe-catalyzed *tert*-alkylative radical Heck-type reactions using *E*/*Z*-mixed internal olefins[10]. In this reaction, a sterically pure internal olefin is not required to diastereoselectively yield the three-substituted olefin. The key to this reaction is the steric bulkiness of the intermediate. In this context, we propose the reactions of α-halocarboxamides and *E*/*Z*-mixed internal olefins via radical processes to generate *trans*-γ-lactams with quaternary carbons (Figure 1d).

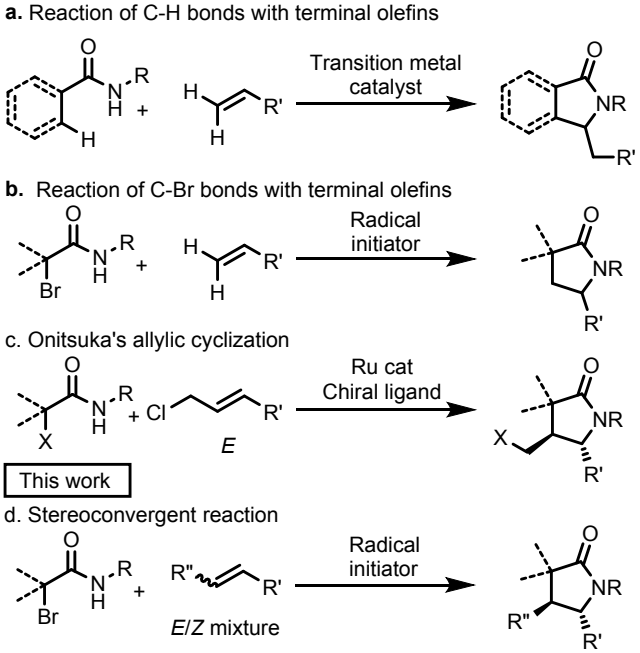

Figure 1. Previous reports and this work

Initially, we attempted the cyclization of α-bromocarboxamide (**1a**) and a styrene derivative (**2a**, *E*:*Z* = 22:78) under our previously reported conditions of Fe-catalyzed *tert*-alkylative Heck-like olefinations with internal olefins[10]. The desired lactam product **3a** was obtained in a 33% yield with *trans* selectivity

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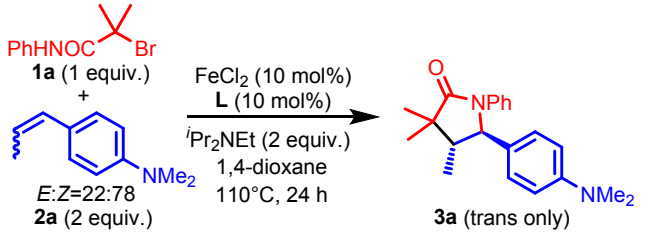
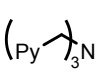
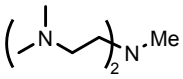
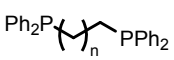
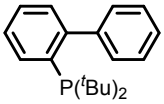
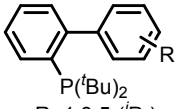
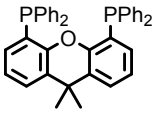
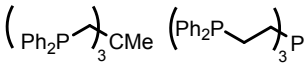
Electronic Supplementary Information (ESI) available: details of experimental procedures, full characterization data, and copies of NMR spectra. See DOI: 10.1039/x0xx00000x

The X-ray crystallographic data used in this study are available in the Cambridge Crystallographic Data Center (CCDC) (Deposition Number 2196246 (3n).

(Table 1), and the reaction may involve a radical process. Therefore, multidentate N ligands that are effective in the generation of α-radicals from α-bromocarbonyls[11,12] were screened (**L1** and **L2**), but this was ineffective. When phosphine ligands were used, the chemical yields improved without loss of selectivity (**L3**–**L13**), e.g., using monophosphines (**L3**, **L4**, **L8**, and **L9**) generated **3a** in yields ranging from 35% to 65%, and using diphosphines generates yields ranging from 36% to 84% (**L5**–**L7**, **L10**, and **L11**). We also evaluated triphosphines (**L12** and **L13**), with the use of **L13** resulting in the optimal yield (89%). All ligands were active at 110 °C only, except **L13**, which remained active at 80 °C. Moreover, **L13** was effective upon decreasing the amount of catalyst employed (5 mol% $FeCl_2$ and 5 mol% of **L13**).

Table 1. Optimization[a]

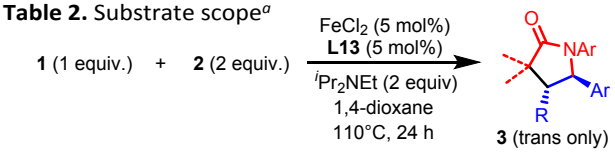


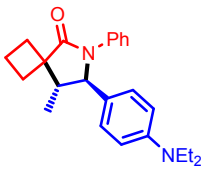
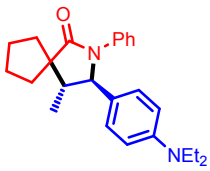
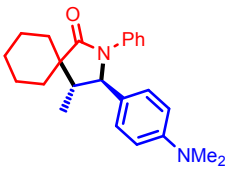
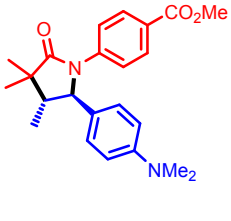
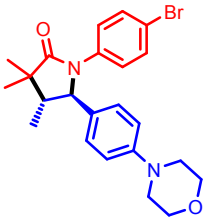
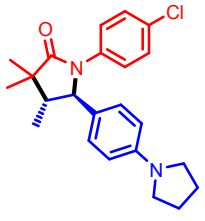
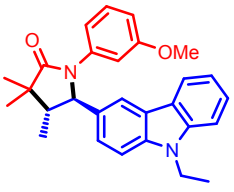
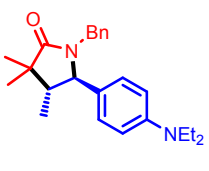
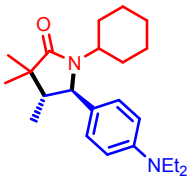
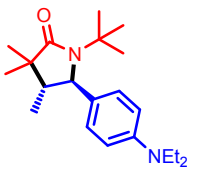
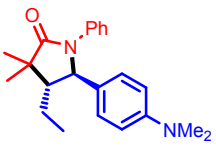
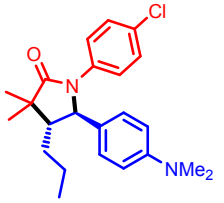
Ligand / GC yield of **3** (%)			
no ligand			PCy3 **L3**: 58
33	**L1**: 11	**L2**: trace	PPh3 **L4**: 55
			
L5 (n= 1): 36 **L6** (n= 2): 52 **L7** (n= 3): 64	**L8**: 65	P(tBu)2 R=1,3,5-(iPr)3 **L9**: 35	
			
L10: 55%	**L11**: 84 (76)[b]	**L12**: 61	**L13**: 89 (84[b]) 72[b,c], 82[d]

[a]A mixture of **1a** (0.50 mmol), **2a** (1.0 mmol), $FeCl_2$ (10 mol%), **L** (10 mol%) and iPrNEt (2 equiv) and 1,4-dioxane was stirred at 110°C for 24 h under N_2. [b]Isolated yield. [c]80°C. [d]$FeCl_2$ (5 mol%) and **L13** (5 mol%).

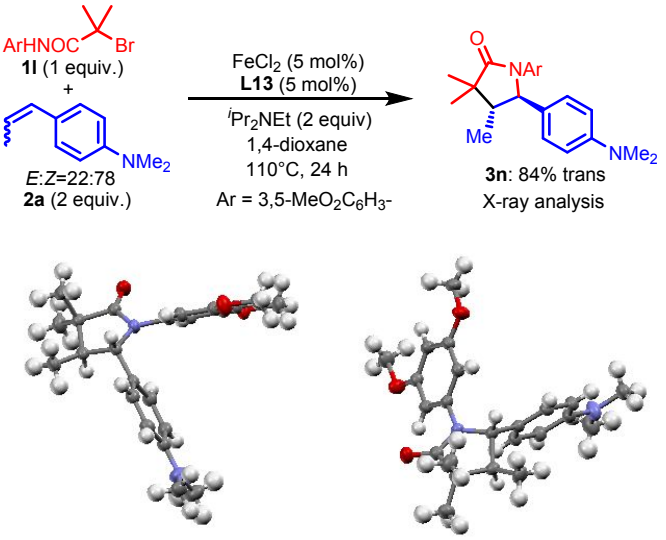
The reactivities of substituted α-bromocarboxamides **1** and styrene derivatives **2** were examined under the optimized reaction conditions (Table 2). Using **1** with cyclic structures (**1b**–**1d**) smoothly generated **3b**–**3d**, with a high yield of lactam **3b**. The scope of *N*-substituents on the aryl group of **2** was very broad, e.g., the reaction of **2** with a cyclic amine (**2c** and **2d**), or heteroaromatic cycle **(2e**) generated **3f** (from **2c**), **3g** (from **2d**), and **3h** (from **2e**) in yields ranging from 72% to 85%. *N*-aryl-substituted α-bromocarboxamides **1** were effective in the reactions, but *N*-alkyl-substituted **1** also underwent cyclization, yielding **3i** and **3j**, respectively. Although the product yield was moderate, even the congested *N*-*tert*-butyl-substituted α-bromocarboxamide **1k** participated in the reaction (40% yield of **3k**). ß-Methyl-substituted **2** generated exclusively *trans*-**3** with a moderate-to-good reactivity, and ß-ethyl- and propyl-substituted styrenes (**2f** and **2g)** also yielded good results. These substrates are more congested than methyl-substituted substrates, but steric hindrance did not affect the selectivities (**3l** and **3m**). But bulkier isopropyl substituted **2** was not reactive. The reasons of the low yields (**3c**, **3d**, **3j**, **3k**) could be the generation of dimers of **1** and Heck-like olefinations. We finally confirmed the trans selectivity of product by X-ray analysis (Scheme 1). When the reaction of **1l** and **2a** was carried out, **3n** was obtained in 84% yield. The X-ray analysis of **3n** showed us trans structure. Trisubstituted olefin **2h** also reacted with **1a** to generate **3o** in a 29% yield (Scheme 2). Although the yield was low, the selectivity was excellent. We also tried stilbene, 3-hexene and methyl cinnamate, but they were not effective.In all cases, the selectivities were perfect and any isomers were not detected.

Table 2. Substrate scope[a]

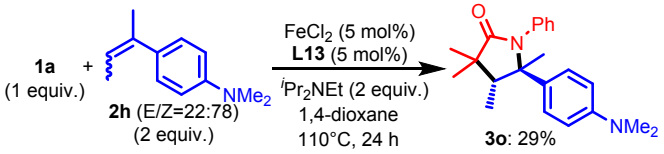


1 / **2** (*E*/*Z*) / Yield of **3** (%)		
		
1b / **2b** (22:78) / **3b**: 80	**1c** / **2b** (22:78) / **3c**: 46	**1d** / **2a** (23:77) / **3d**: 39
		
1e / **2a** (23:77) / **3e**: 84	**1f** / **2c** (21:79) / **3f**: 85	**1g** / **2d** (62:38) / **3g**: 72
		
1h / **2e** (30:70) / **3h**: 74	**1i** / **2b** (22:78) / **3i**: 77	**1j** / **2b** (22:78) / **3j**: 59
		
1k / **2b** (22:78) / **3k**: 40	**1a** / **2f** (13:87) / **3l**: 65	**1g** / **2g** (12:88) / **3m**: 60

[a]A mixture of **1** (0.50 mmol), **2** (1.0 mmol), $FeCl_2$ (5 mol%), **L13** (5 mol%) and iPrNEt (2 equiv) and 1,4-dioxane was stirred at 110°C for 24 h under N_2.



Scheme 1 X-ray structure of **3n**



Scheme 2 The reaction with trisubstituted **2h**.

Subsequently, control experiments were performed to determine the reaction mechanism (Figure 2). First, we studied the reaction in the presence of TEMPO, which is a simple radical inhibitor (Figure 2#1). No product was obtained, indicating that this reaction involves a radical process. The formation of a C–N bond at the end of the catalytic cycle may proceed via an intramolecular S_N1-like reaction via a cationic species. Therefore, we attempted to trap the cationic species using benzyl alcohol[13], but no trace of **3a-OR** was obtained (Figure 2#2). Therefore, the final C–N bond formation may occur via reductive elimination from metallacycle **D**, as shown in Figure 3. Additionally, we expected that the high diastereoselectivity observed should be due to olefin isomerization. Therefore, we investigated the potential isomerization of **2a** under the optimized conditions. However, no isomerization of **2a** was observed (Figure 2#3), and the reactivities of (*E*)- and (*Z*)-**2a** were comparable (Figure 2#4).

Considering the control experiments, we propose a possible reaction mechanism, as shown in Figure 3. The reaction commences with the generation of tertiary alkyl radical species **A** by the reaction between the Fe salt and **1**. In this reaction, electron-rich olefins were required because generated alpha radical **A** is electrophilic. Subsequently, the addition of **A** to **2** occurs to yield radical intermediate **B**. Intermediate **C**, which is generated from oxidation of **B** with iron salt, undergoes oxidative cyclization with Fe to generate metallacycle **D**. To avoid steric repulsion between R^4 and the Ar group of **2**, **C** adopts a *trans* conformation. Finally, lactam **3** is formed via the reductive elimination of **D**.

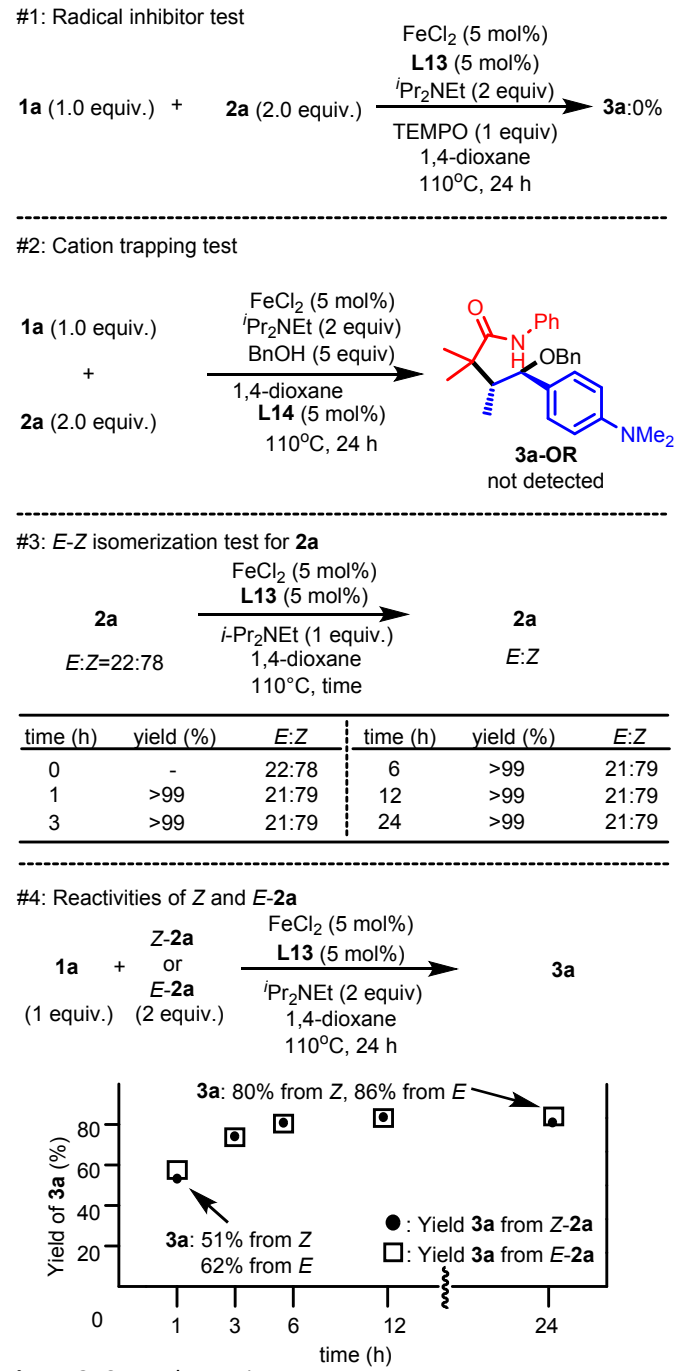


Figure 2. Control experiments

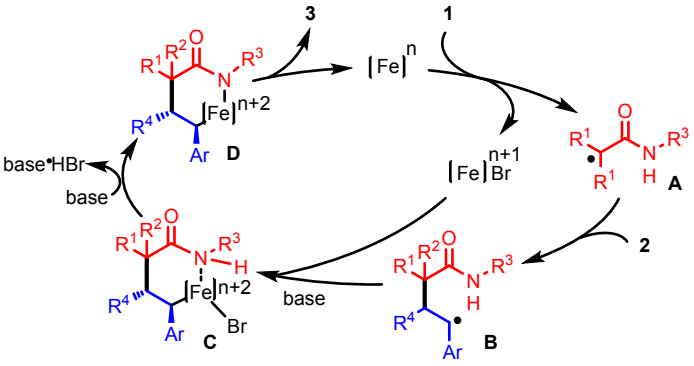


Figure 3. Proposed mechanism

Conclusions

In conclusion, highly selective lactamization reactions were conducted using the Fe catalyst system. Our methodology does not require sterically pure internal olefins, which are not easily available. The key to this selective reaction is the use of the Fe/triphos catalyst system. Although the reason of the *trans* selectivity remains unclear, the selective generation of metallacycle **C** may be critical. Further investigations, including the asymmetric version of this reaction, shall be reported by our group.

We warmly thank Yamaguchi University, JST SPRING Grant Number JPMJSP2111, JSPS Grants-in-Aid for Scientific Research (B) Grant Number 21H01939, and JSPS KAKENHI Grant Number JP20H04823 in Hybrid Catalysis for Enabling Molecular Synthesis on Demand.

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