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RESEARCH ARTICLE

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trans-Selective Aryldifluoroalkylation of Endocyclic Enecarbamates and Enamides via Nickel Catalysis

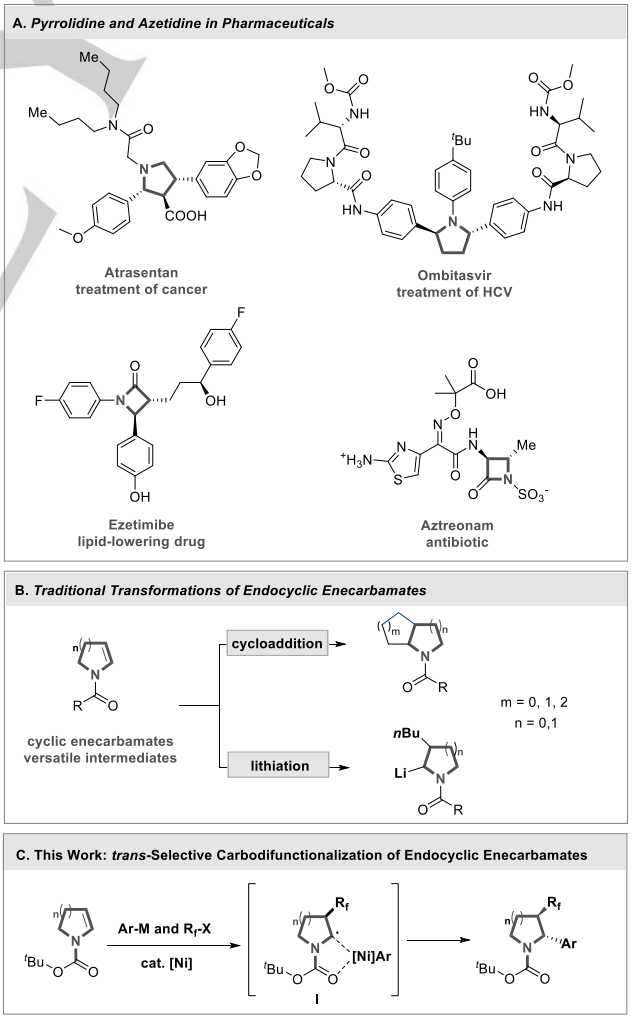
Chang Xu, Ran Cheng, Yun-Cheng Luo, Ming-Kuan Wang, and Xingang Zhang*

Dedicated to the 70th anniversary of Shanghai Institute of Organic Chemistry

Abstract: 2-Pyrroline and 2-azetine are useful synthons for the synthesis of pyrrolidines and azetidines that widely exist in natural products, pharmaceuticals, and agrochemicals. But efficient methods for dicarbofuntionalization of these cyclic alkenes are limited. Particularly, the dicarbofunctionalization of endocyclic enecarbamates to achieve fluorinated compounds remains an unsolved issue, despite of the wide applications of organofluorinated molecules in life and materials science. Here, we report a nickel-catalyzed *trans*-selective dicarbofunctionalization of *N*-Boc-2-pyrroline and *N*-Boc-2-azetine, a class of endocyclic enecarbamates previously unexplored by transition-metal catalyzed dicarbofunctionalization. The reaction can also extend to six and seven membered endocyclic enamides. A variety of arylzinc reagents and bromodifluoroacetate and its derivatives are applicable to the reaction, providing a straightforward and efficient access to an array of pyrrolidine- and azetidine-containing fluorinated amino acids and oligopeptides, which may have applications in life science. Specifically, this protocol paves a new way to the efficient synthesis of functionalized azetidines that are of great interest in pharmacological studies.

Introduction

Pyrrolidines and azetidines are a class of *N*-heterocycles scaffold that widely exist in natural products, pharmaceuticals and agrochemicals (with examples shown in Scheme 1A).[1] The five and four-membered endocyclic enecarbamates are versatile synthons for the synthesis of structurally diversified pyrrolidines and azetidines through transformations of their carbon-carbon double bonds. In particular, the dicarbofunctionalization of these endocyclic alkenes can result in molecular complexity and diversity. Two general methods via this strategy have been developed (Scheme 1B): one is cycloaddition reactions, including [4+2], [3+2], and photo-induced [2+2] cycloaddition;[2] the other is the lithiation of endocyclic enecarbamates with strong base *n*-BuLi, followed by reaction with an electrophile.[3] These two methods are useful and have been applied in the synthesis of alkaloids natural products and bioactive compounds. [2-4] However, the former is only effective for the construction of bicyclic structures, and the latter has limited functional group tolerance due to the use of strong base. Although a tandem radical alkynyltrifluoromethylation of 2-pyrroline has been reported recently, the reaction was limited to silyl alkyne-derived triflone and Togni's reagent, thus restricting its wide-spread synthetic applications.[5] Particularly, these methods remain inadequately explored in the synthesis of functionalized four-membered azetidines,[6] which are largely required in pharmacological studies.[7] Hence, new efficient methods to functionalized pyrrolidines and azetidines are highly desirable.



Scheme 1. Approaches to functionalized pyrrolidines and azetidines through transformations of endocyclic enecarbamates and selected pharmaceuticals containing functionalized pyrrolidine and azetidine motifs.

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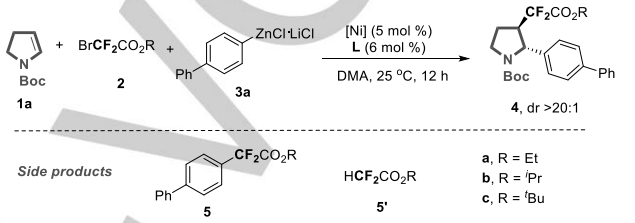
Very recently, we have developed a nickel-catalyzed three-component dicarbofunctionalization of enamides through a chelation assisted strategy.[8] We envisioned that similar nickel-catalyzed process would be a promising complement to the synthesis of dicarbofunctionalized pyrrolidines and azetidines (Scheme 1C). Although the nickel-catalyzed three-component dicarbofunctionalization reactions have received increased attention, most of these developed methods focus on the corresponding reaction of terminal alkenes,[9] and only a few examples involve internal alkenes or endocyclic alkenes, such as norbornenes.[10] Example of transition-metal catalyzed multicomponent dicarbofunctionalization of endocyclic enecarbamates has not been reported yet.[11] In particular, dicarbofunctionalization of these alkenes to achieve fluorinated compounds remains an unsolved issue, although such a strategy is straightforward to provide fluorinated molecules with tunable structural complexity to discover interesting new bioactive molecules used as pharmaceuticals and agrochemicals.[12] The synthetic route, as proposed in Scheme 1C, can overcome the aforementioned limitations and install two different components across a double bond selectively from one-pot synthesis. In particular, this route would provide an efficient and straightforward access to the strained functionalized azetidines. In this nickel-catalyzed process, the carbonyl moiety on the endocyclic enecarbamates may function as a chelating group to facilitate the recombination of nickel species with the carbon center and suppress the β-hydride elimination, thus promote the overall catalytic cycle.

Results and Discussion

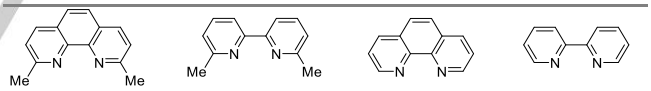
Development of the Reaction

To test our hypothesis, we chose *N*-Boc-2-pyrroline **1a**, commercially available $BrCF_2CO_2Et$ **2a**, and arylzinc reagent **3a** as the model substrates (Table 1). The use of **2a** is because of its low cost and the synthetic versatility of CO_2Et moiety. Additionally, the incorporation of CF_2 group into organic molecules often improves the dipole moments, changes the conformations, and increases the acidity of the neighboring group adjacent to the CF_2 compared to their non-fluorinated counter parts.[13] Most importantly, the resulting fluorinated amino acids may provide a good opportunity for design of peptide based bioactive molecules.[14] After a survey of a series of reaction parameters, such as ligand and nickel sources, we found that the steric effect of the tested ligands dramatically influenced the reaction efficiency (for details, see the Supporting Information). The combination of $NiCl_2$·DME (5 mol%) with sterically hindered 1,10-phenanthroline (phen)-based ligand **L1** could provide the desired product **4a**, dicarbofunctionalized pyrrolidine, in 45% yield with a high *trans*-selectivity (dr > 20:1) (entry 1). A comparable yield of **4a** with high *trans*-selectivity was also obtained by using a bulky ligand 6,6'-dimethyl-2,2'-bipyridine **L2** (entry 2). Non-sterically hindered phen- and bypyridine (bpy)-based ligands resulted in lower yields of **4a** due to the severe formation of cross-coupling side product **5a** (entries 3 and 4, for details, see the Supporting Information). Among the tested nickel salts, $NiCl_2$ showed similar activity as $NiCl_2$·DME (entry 5). While, using NiI_2 could improve the yield of **4a** to 57% (entry 6). Further optimization of the reaction conditions by increasing the steric hindrance of **2a** benefits the reaction efficiency (entries 7 and 8), and an 80% yield of **4c** upon isolation could be obtained with **2c** as the substrate (entry 8). The use of bulky *tert*-butyl ester probably sterically prevents its decomposition in the reaction, as severe defluorination side reaction was observed when **2a** was used.[15] No desired product was observed in the absence of nickel (entry 9), and only 14% yield of **4a** was obtained without **L1** (entry 10). In addition to nickel catalysts, the cobalt catalysts were also examined.[16] However, only ~10% yield of desired product **4** was observed (see the Supporting Information). Thus, these results demonstrate the critical role of [Ni/**L**] in promoting the dicarbofunctionalization of endocyclic enecarbamates.

Table 1. Representative results for optimization of Ni-catalyzed aryldifluoroalkylation of endocyclic enecarbamates **1a** [a]



Entry	[Ni]	ligand	R	Yield [%][b] 4	5	5'
1	$NiCl_2$·DME	**L1**	Et	**4a**, 45	**5a**, 19	**5a'**, 1
2	$NiCl_2$·DME	**L2**	Et	**4a**, 41	**5a**, 19	**5a'**, 2
3	$NiCl_2$·DME	**L3**	Et	**4a**, 33	**5a**, 58	**5a'**, 0
4	$NiCl_2$·DME	**L4**	Et	**4a**, 20	**5a**, 71	**5a'**, 0
5	$NiCl_2$	**L1**	Et	**4a**, 44	**5a**, 11	**5a'**, 8
6	NiI_2	**L1**	Et	**4a**, 57	**5a**, 13	**5a'**, 1
7	NiI_2	**L1**	*i*Pr	**4b**, 69	**5b**, 21	**5b'**, 3
8	NiI_2	**L1**	*t*Bu	**4c**, (80)[c]	**5c**, 11	**5c'**, 2
9	none	**L1**	*t*Bu	**4c**, 0	**5c**, 0	**5c'**, 1
10	NiI_2	none	*t*Bu	**4c**, 14	**5c**, 1	**5c'**, 7

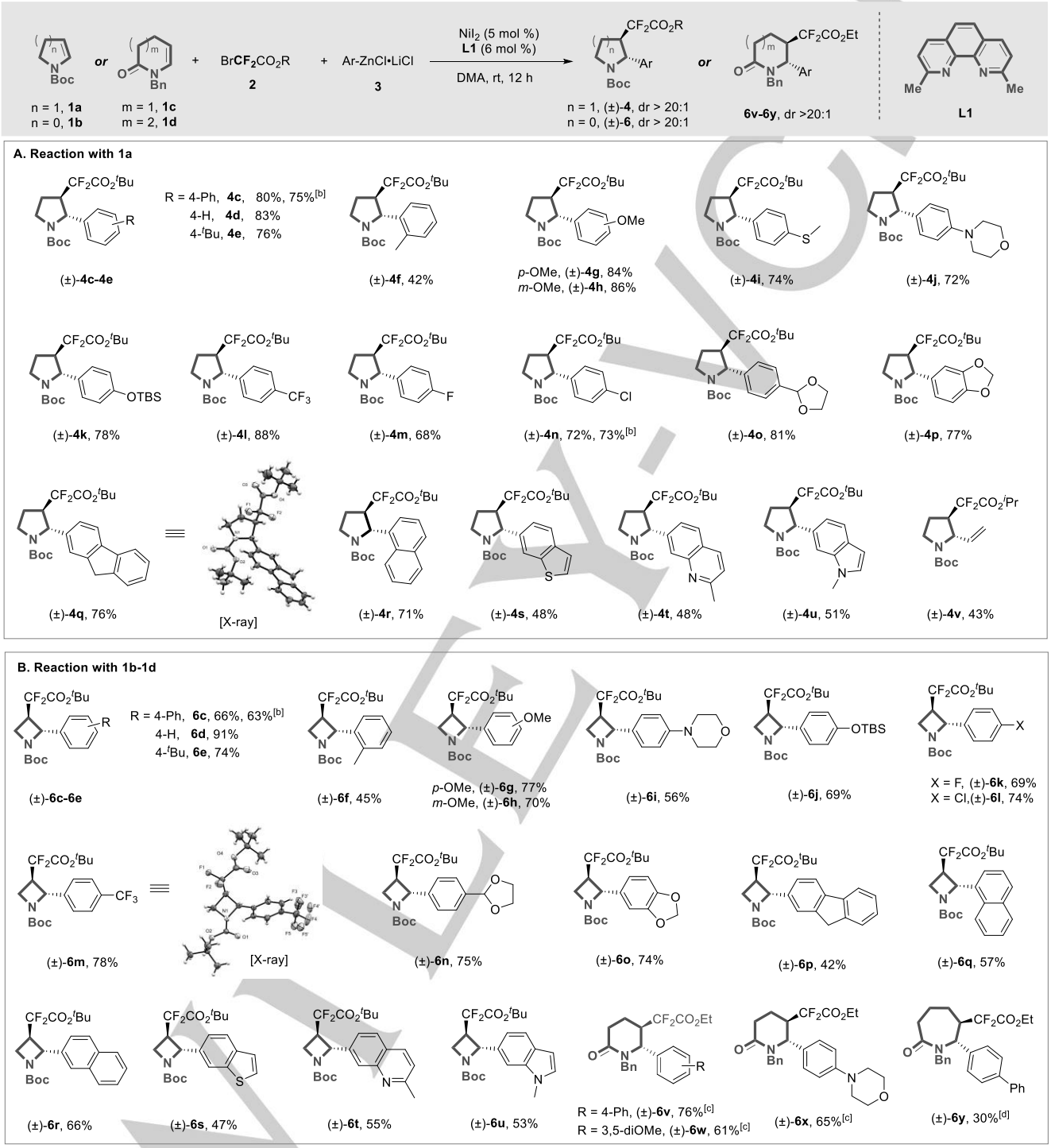


[a] Reaction conditions (unless otherwise specified): **1a** (0.4 mmol, 1.0 equiv), **2** (1.5 equiv), **3a** (1.5 equiv in THF), and DMA (2 mL). [b] Determined by ^{19}F NMR using benzotrifluoride as an internal standard; the number given in the parentheses is the isolated yield. [c] The diastereoselectivity of **4c** is > 20:1 determined by both ^{19}F NMR and ^{1}H NMR after deprotection of Boc by $Sn(OTf)_2$.

Substrate Scope and Synthetic Application

With the viable reaction conditions in hand, a series of arylzinc reagents were examined for the dicarbofunctionalization of **1a** with **2c** (Scheme 2A). Generally, high *trans*-selectivity (dr > 20:1) and moderate to high yields of **4** were obtained. The nucleophilic nature of arylzinc reagents did not interfere with the reaction efficiency. Substrates bearing electron-donating or electron-withdrawing groups all provided the corresponding products with high efficiency (**4g**-**4o**). The steric arylzinc reagents were also applicable to the reaction and furnished the corresponding products smoothly (**4f** and **4r**). The reaction exhibited good functional group tolerance. Important functional moieties, such as thioether, morpholine, silylether, dioxolane, even aryl chloride, were compatible with the reaction conditions (**4i**-**4k**, **4n**, **4o**). Polycyclic aromatic ring-containing substrate (**4q**) and a series of heteroarenes, including benzothiophene, quinoline, and indole, were also amenable to

the reaction (**4s**-**4u**). Furthermore, vinylzinc reagent was also a suitable substrate, providing the corresponding product **4v** in 43% yield with isopropyl ester **2b** as a coupling partner. However, no reaction occurred with alkynylzinc as the nucleophiles due to the severe decomposition of bromodifluoroacetate **2**.

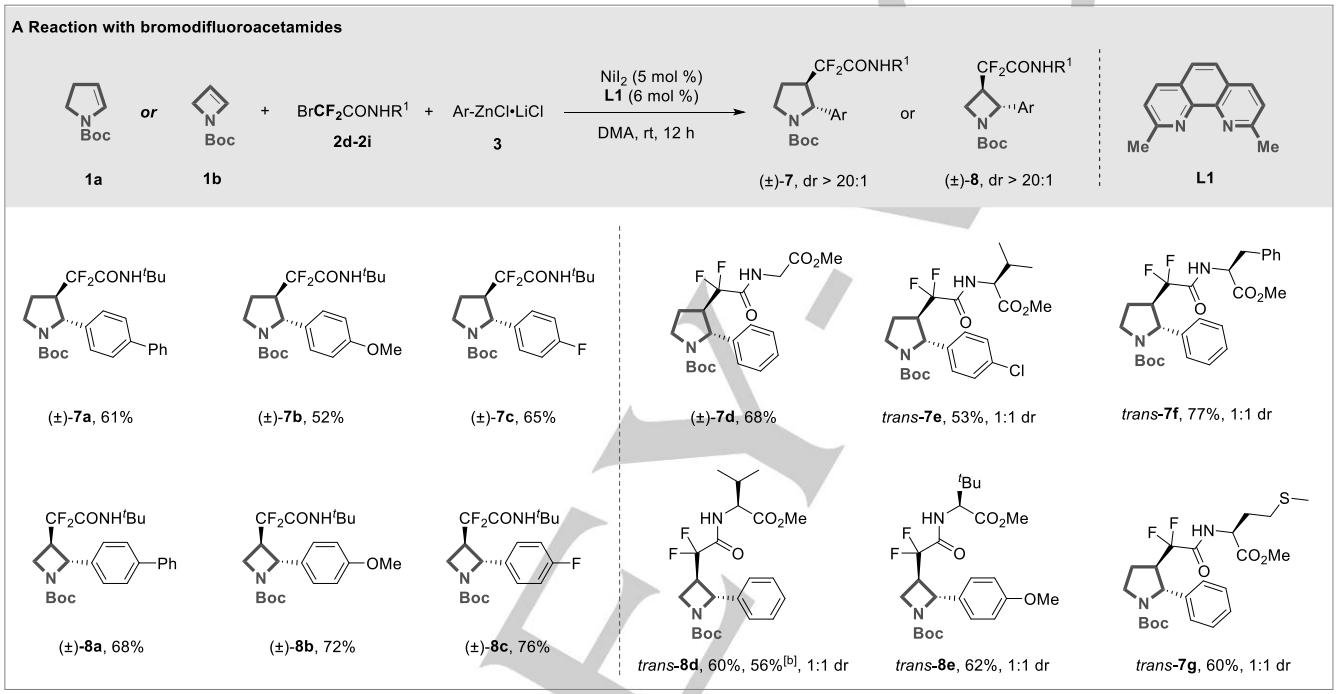


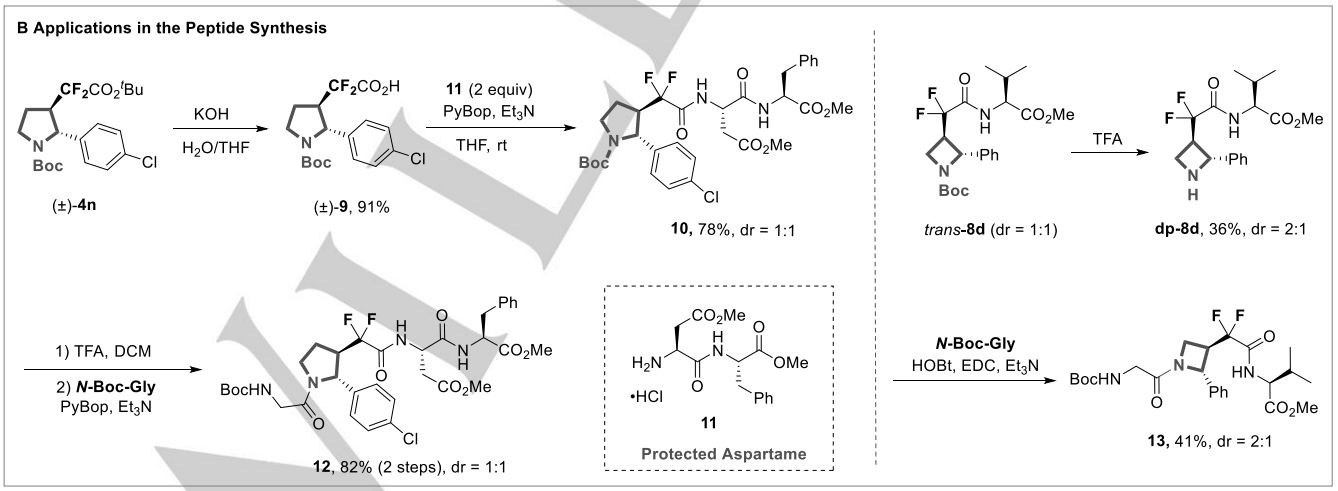
Scheme 2. Scope of the Nickel-Catalyzed Aryldifluoroalkylation of Endocyclic Enecarbamates[a] [a] Reaction conditions (unless otherwise specified): **1** (0.4 mmol, 1.0 equiv), **2** (1.5 equiv), **3** (1.5 equiv in THF), and DMA (2 mL). Isolated yields are given. Diastereomeric ratios were determined by ^{19}F NMR analysis. [b] Gram-scale synthesis. [c] **2a** was used and the reaction was conducted without **L1**. [d] 2.5 equiv of **2a** (2.5 equiv) and 2.0 equiv of **3a** were used and the reaction was conducted without **L1**.

Notably, the strained four-membered ring did not affect the reactivity of 2-azetine **1b**, and allowed this nickel-catalyzed tandem process with a series of arylzinc reagents efficiently (Scheme 2B). An array of dicarbofunctionalized azetidines **6**, which are difficult to access through conventional methods,[3b, 3c,6] could be achieved through this transformation with high efficiency and *trans*-selectivity (dr > 20:1). Similarly, good functional group tolerance was observed (**6i**, **6j**, **6n**), even toward aryl chloride and heteroarenes (**6l**, **6s**-**6u**). The reaction can also extend to six and seven membered endocyclic enamides, where *N*-Bn dihydropyridinone and seven membered enamide furnished the corresponding products smoothly (**6v**-**6y**) without the need of **L1**, thus demonstrating the generality of this protocol. The reaction can be readily

scalable, as demonstrated by the gram-scale synthesis of **4c**, **4n**, and **6c** with comparable yields. The *trans*-configuration of the resulting products **4** and **6** was assigned by the single-crystal X-ray diffraction studies of **4q** and **6m**.[17]

In addition to bromodifluoroacetate, bromodifluoroacetamides were also applicable to the reaction, and provided a series of pyrrolidine- and azetidine-based difluoroacetamides with high efficiency and high *trans*-selectivity (dr > 20:1) (Scheme 3A). Most remarkably, a variety of amino acids, including glycine, valine, phenylanaline, and 2-amino-3,3-dimethylbutanoic acid derived bromodifluoroacetamides were applicable to the reaction, providing the corresponding dipeptides efficiently (**7d**-**7f**, **8d**, **8e**). Even the methionine-containing substrate underwent the present process smoothly without poisoning the nickel catalyst (**7g**). Although 1:1 diastereoselectivity was observed, these resulting dipeptides (**7d**-7**g**, **8d**, **8e**) are of great interest in chemical biology, in light of the unique properties of CF_2[13] and significant biological properties of pyrrolidine and azetidine scaffolds[1c, 1d, 5b], which are limited in availability owing to the lack of efficient synthetic methods. Importantly, the present synthesis of these dipeptides can also be scalable as demonstrated by the synthesis of azetidine-containing dipeptide *trans*-**8d**, featuring the practicability of this approach.





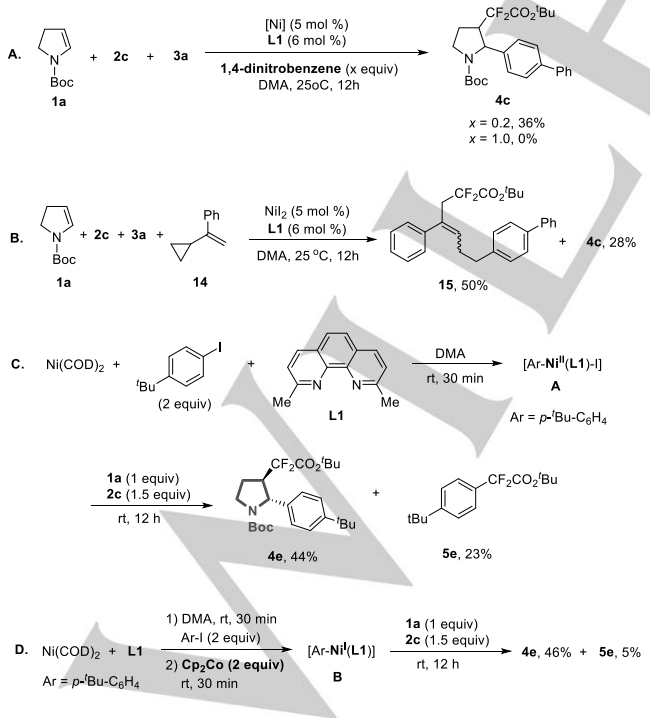
Scheme 3. Reaction with Bromodifluoroacetamides and Synthesis of Peptides. **A.** Scope of Bromodifluoroacetamides.[a] [a] Reaction conditions (unless otherwise specified): **1a** or **1b** (0.4 mmol, 1.0 equiv), **2** (1.5 equiv), **3** (1.5 equiv in THF), and DMA (2 mL). Isolated yields are given. Diastereomeric ratios were determined by ^{19}F NMR or ^{1}H NMR analysis. [b] Gram-scale synthesis. **B.** Applications in the Synthesis of Peptides..

The resulting compounds **4** and **6** can serve as useful building blocks for the synthesis of fluorinated peptides. As shown in Scheme 3B, selective deprotection of *tert*-butyl ester on the racemic **4n** by alkaline hydrolysis led to acid **9** in high yield (91%). Condensation of **9** with aspartame-based dipeptide **11** efficiently provided the fluorinated tripeptide **10** (78% yield) with 1:1 dr. Subsequently, deprotection of *N*-Boc with TFA, followed by the second condensation with *N*-Boc-glycine afforded tetrapeptide **12** in 82% overall yield (2 steps) (dr = 1:1). Furthermore, the resultant dipeptides **7** and **8** can also be used for the peptide elongation. For example, deprotection of *N*-Boc on dipeptide *trans*-**8d**, followed by condensation with *N*-Boc-glycine produced the tripeptide **13** in synthetic useful yield with 2:1 dr. The low yields of **dp-8d** and **13** are because of forming some uncertain byproducts. Since the incorporation of fluorine atom(s) into the peptides can result in unexpected effects and

the rigidity of pyrrolidine and azetidine can determine the conformation of peptides and the structure of protein,[18] the present process may provide opportunities for potential applications in discovering new peptide-based bioactive molecules or in peptide and protein engineering.

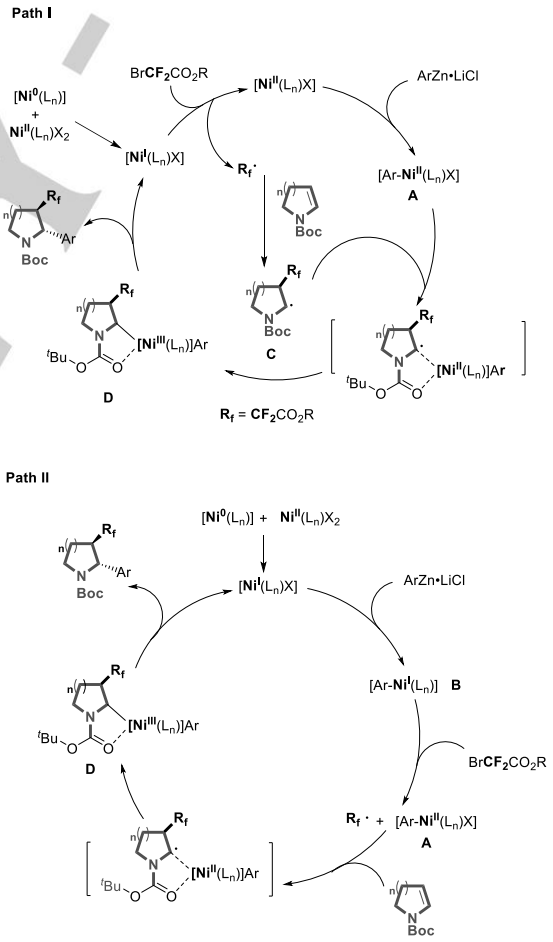
Mechanistic Studies

To gain mechanistic insight into the reaction, several experiments were conducted. Radical inhibition experiment with 1,4-dinitrobenzene as the electron transfer inhibitor[19] and radical clock experiment with α-cyclopropylstyrene **14**[20] as the probe indicated that a difluoroacetyl radical generated *in situ* via a single electron transfer (SET) pathway was likely involved in the reaction (Scheme 4A and 4B). We also prepared [Ar-Ni^{II}(**L1**)] complex (**A**) *in situ* with **L1** as the ligand (Scheme 4C).[21] Treatment of complex **A** with **1a** and **2c** afforded the pyrrolidine **4e** in 44% yield along with 23% yield of cross-coupling side product **5e**. Meanwhile, a parallel reaction by reduction of [Ar-Ni^{II}(**L1**)] (**A)** with Cp_2Co[22] was performed to generate [Ar-Ni^{I}(**L1**)] complex (**B**) (Scheme 4D). The formation of complex **B** was supported by the EPR analysis of the reaction, in which the EPR signal of complex **B** is similar with the nickel(I) complex reported in the literature[23] (Supporting Information Figure S2). However, no EPR signal was observed in the absence of reductant Cp_2Co (Supporting Information Figure S1), suggesting that two different nickel species were involved in these two reactions. Addition of **1a** and **2c** to the solution of [Ar-Ni^{I}(**L1**)] (**B**) also led to **4e** with a comparable yield, but the side product **5e** was dramatically suppressed (Scheme 4D). These results suggested that both [Ar-Ni^{II}(**L1**)] and [Ar-Ni^{I}(**L1**)] are likely the active nickel species in the catalytic cycle.



Scheme 4. Mechanistic studies

On the basis of above results and previous reports,[8, 23a, 24] two possible pathways via Ni(I/III) catalytic cycle were proposed. **Path I** (Scheme 5): the reaction began with the formation a nickel(I) species through the comproportionation of Ni(II) and *in-situ* generated Ni(0).[25] This [Ni^{I}] species subsequently reacted with bromodifluoroacetate through a SET reaction to produce the nickel(II) and difluoroacetyl radical, which was trapped by the alkene to generate a new alkyl radical **C**. Meanwhile, transmetallation of nickel(II) with arylzinc reagent provided [Ar-Ni^{II}(L$_n$)X] complex **A**. **A** reacted with **C** with the aid of chelating carbonyl group on the enecarbamate or enamides[8] to give the key intermediate nickel(III) **D**. In the case of 2-azetine **1b**, the carbonyl group on the ring might not chelate with nickel(II) species **A** due to the ring strength of four membered ring. Finally, reductive elimination of **D** produced the final product and regenerated [Ni^{I}] simultaneously. **Path II** (Scheme 5): The reaction was initiated by the formation of [Ar-Ni^{I}(L$_n$)] complex **B** between arylzinc reagent and [Ni^{I}]. Subsequently, **B** reacted with bromodifluoroacetate to produce the [Ar-Ni^{II}(L$_n$)X] **A** and difluoroacetyl radical, which was trapped by enecarbamate to give a new alkyl radical **C**. Recombination of **A** with **C** with the aid of chelating carbonyl group afforded the key intermediate **D**. **D** underwent reductive elimination to give the final product and regenerate [Ni^{I}].



Scheme 5. Proposed reaction mechanism

Conclusion

In conclusion, we have developed an efficient method to synthesize dicarbofunctionalized pyrrolidines and azetidines via nickel catalysis. The reaction can also extend to six and seven membered endocyclic enamides. This nickel-catalyzed radical tandem process enables a series of arylzinc reagents and bromodifluoroacetate and its derivatives to *trans*-selectively

functionalize these endocyclic alkenes. In particular, the successful aryldifluoroalkylation of four-membered, strained 2-azetine provides a straightforward and efficient access to azetidines of pharmaceutical interests. The reaction exhibited high functional group tolerance, even toward a series of amino acid-containing substrates. The resulting four- and five-membered difluorinated amino acids as well as the fluorinated dipeptides can serve as useful building blocks for peptide synthesis, providing opportunities for applications in chemical biology and medicinal chemistry. This nickel-catalyzed radical tandem process also paves a new way to harness the endocyclic enecarbamates and enamides, particularly, 2-azetine, for efficient transformations.

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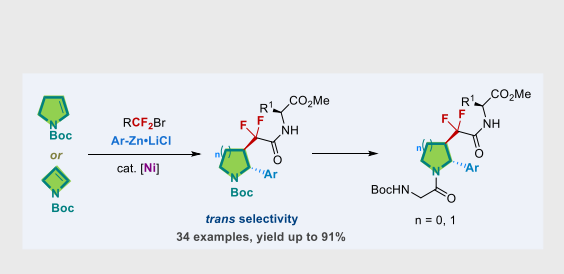

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trans-Selective Aryldifluoroalkylation of Endocyclic Enecarbamates and Enamides via Nickel Catalysis

Simplicity and Efficiency: A nickel-catalyzed dicarbofunctionalization of endocyclic enecarbamates and enamides has been developed. This tandem reaction provides a straightforward and efficient access to an array of pyrrolidine- and azetidine-containing fluorinated amino acids and oligopeptides, which may have applications in life science. Specifically, this protocol paves a new way to the efficient synthesis of functionalized azetidines that are of great interest in pharmacological studies.