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Synthesis of Tetra-Substituted Trifluoromethyl-3,1-Benzoxazines by Transition-Metal-Catalyzed Decarboxylative Cyclization of *N*-Benzoyl Benzoxazinones

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Efficient synthesis of *N*,*O*-heterocyclic tetra-substituted trifluoromethyl-3,1-benzoxazines via a transition-metal-catalyzed decarboxylative intramolecular cyclization was achieved. The decarboxylation of *N*-benzoyl trifluoromethyl-benzoxazinones generated the amide oxygen nucleophile, allowing a selective internal C_1-attack on Pd- or Cu-coordinated zwitterions, affording medicinally attractive tetra-substituted vinyl- or ethynyl-trifluoromethyl-3,1-benzoxazines. This protocol can be applied to the synthesis of perfluoroalkyl- and non-fluorinated 3,1-benzoxazines.

Fluorinated *N*-heterocyclic compounds have been in a promising position of drug development in pharmaceuticals[1] or agrochemicals[2] since the discovery of fluorinated quinolones.[3] In particular, trifluoromethylated *N*,*O*-containing six-membered heterocycles have become primary synthetic targets in recent drug discovery due to their great market success.[4] A representative example is the anti-HIV drug, efavirenz,[5] which has an *N*,*O*-heterocyclic 3,1-benzoxazine structure with a tetra-substituted trifluoromethyl C_{sp3} center (Figure 1). Thus, the development of an efficient synthetic methodology for trifluoromethylated *N*,*O*-heterocyclic compounds is highly desirable. Besides, *N*,*O*-heterocyclic 3,1-benzoxazines with a tetra-substituted C_{sp3} center are privileged structures of biologically active molecules (Figure 1).[6] In this context, many chemists have focused on the development of efficient synthetic methods to synthesize *N*,*O*-heterocyclic 3,1-benzoxazine structures with a tetra-substituted C_{sp3} center.[7] However, the synthesis of a *N*,*O*-heterocyclic 3,1-benzoxazine structure with a tetra-substituted trifluoromethyl C_{sp3} center remains a challenge.[8]

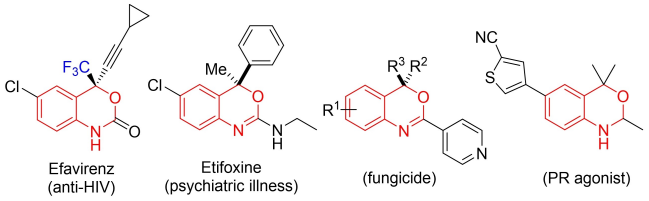

Figure 1. Bioactive *N*,*O*-heterocyclic 3,1-benzoxazines.

In the last few decades, the transition-metal-catalyzed cycloaddition reaction of zwitterion intermediates has emerged as a powerful method for constructing various *N*-heterocyclic compounds.[9] *N*-Toluene sulfonyl (tosyl) 4-vinyl benzoxazinones[10] and *N*-tosyl 4-ethynyl benzoxazinones[11] are two representative substrates in this area that have been widely used for many types of annulation reactions under metal catalysis, Pd for 4-vinyl and Cu for 4-ethynyl substrates. The decarboxylative generation of zwitterionic π-allyl-Pd or Cu-allenylidene intermediates, which serve as crucial reactive species for the annulation reactions, are promptly trapped intermolecularly by a variety of interceptors.[9–11] *N*-Tosyl 4-trifluoromethyl-benzoxazinones have recently joined this research area (Scheme 1a),[12] and a couple of novel annulation reactions have been disclosed under Pd-catalysis. π-Benzyl-Pd zwitterionic intermediates generated via decarboxylation have been suggested as reactive species,[12a,b] and unique trifluoromethylated *N*-heterocycles are synthesized in good to high yields. In 2019, we revealed that medicinally attractive trifluoromethyl-dihydroquinoline derivatives are obtained in good yields by the decarboxylative intramolecular annulation of *N*-tosyl 4-vinyl-4-trifluoromethyl benzoxazinones in the presence of Pd-catalysts (Scheme 1b).[13] The intramolecular C_3-attack by tosyl amide-nitrogen is the key to the cyclization reaction. During the decarboxylative annulation reactions,[12–14] we noticed the critical role of the *N*-tosyl-moiety in a series of benzoxazinones for annulation reactions, while *N*-benzoyl-variants furnished completely different products. In a seminal paper by Tunge in 2009, a single example of 3,1-benzoxazine

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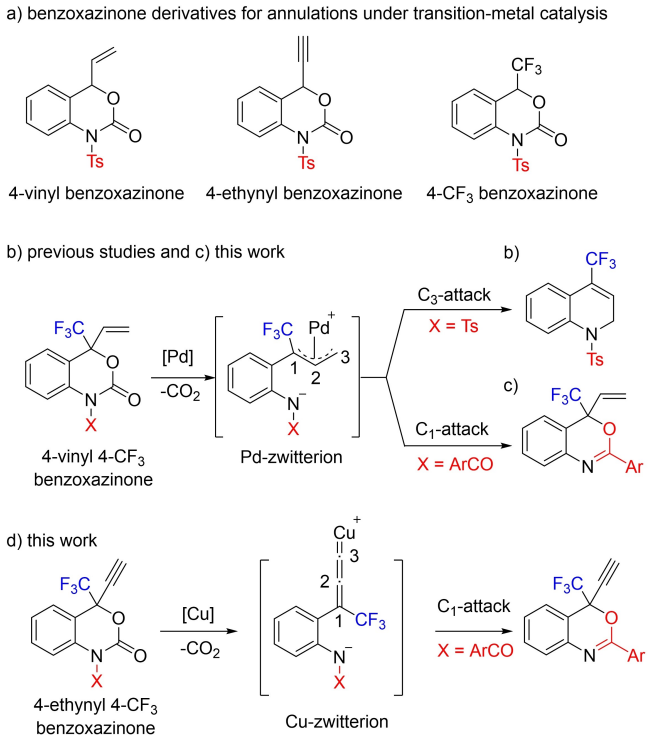
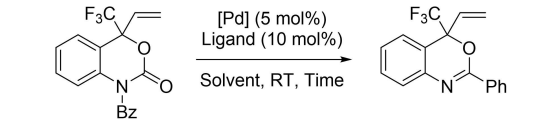
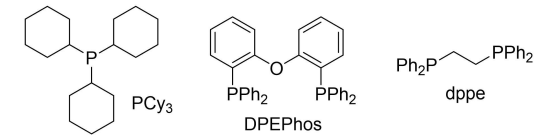


Scheme 1. Synthesis of heterocycles from benzoxazinones: a) Three benzoxazinone derivatives for annulation reactions. b) Annulation reaction of *N*-tosyl 4-vinyl-4-trifluoromethyl benzoxazinones under Pd-catalysis (previous work). c) Annulation reaction of *N*-benzoyl 4-vinyl-4-trifluoromethyl benzoxazinones under Pd-catalysis (this work). d) Annulation reaction of *N*-benzoyl 4-ethynyl-4-trifluoromethyl benzoxazinones under Cu-catalysis (this work).

Table 1. Optimization of reaction conditions for vinyl-benzoxazinones.[a]



Ligand



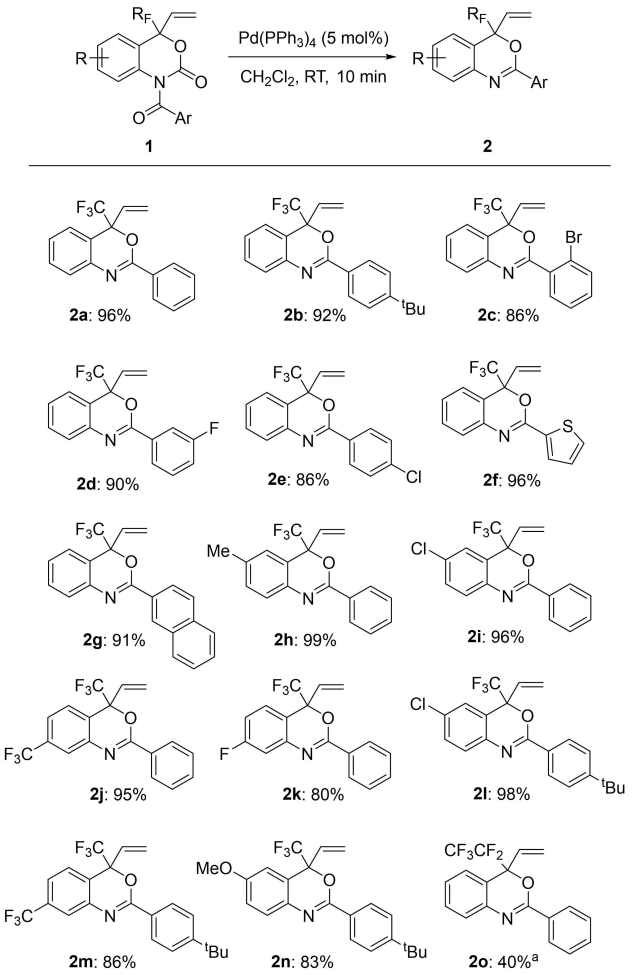
Entry	[Pd]	Ligand	Solvent	Time	Yield/%[b]
1	$Pd(PPh_3)_4$	–	CH_2Cl_2	10 min	99
2	$Pd_2(dba)_3{\cdot}CHCl_3$	PCy_3	CH_2Cl_2	20 h	8
3	$Pd_2(dba)_3{\cdot}CHCl_3$	DPEPhos	CH_2Cl_2	20 h	98
4	$Pd_2(dba)_3{\cdot}CHCl_3$	dppe	CH_2Cl_2	20 h	88
5	$Pd(PPh_3)_4$	–	Toluene	17.5 h	98
6	$Pd(PPh_3)_4$	–	THF	4.5 h	96
7	$Pd(PPh_3)_4$	–	DMF	10 min	96

[a] Reaction was carried out with **1a** (0.05 mmol), [Pd] (5 mol%), ligand (10 mol%) in CH_2Cl_2 (0.5 mL) at room temperature. [b] Determined by ^{19}F NMR in crude using $PhCF_3$ as an internal standard.

synthesis from *N*-benzoyl 4-vinyl benzoxazinone under Pd-catalysis was shown.[10b] However, the substrate scope and generality were entirely unexplored, despite their potential applications. Herein, we report the efficient synthesis of *N,O*-heterocyclic tetra-substituted trifluoromethyl-3,1-benzoxazines by the transition-metal-catalyzed decarboxylative intramolecular cyclization of 4-vinyl or 4-ethynyl 4-trifluoromethyl-benzoxazinones in good to high yields. Independent of the substitution of the 4-vinyl or the 4-ethynyl group, the amide oxygen of the benzoyl moiety attacks at the C_1-position of trifluoromethyl-substituted Pd-π-allyl or Cu-allenylidene zwitterions to generate a tetra-substituted trifluoromethyl C_{sp3}-stereogenic center in the *N,O*-heterocyclic skeleton. While there is much effort on synthesizing *N,O*-heterocyclic 3,1-benzoxazine structures,[7–8] no general method for the synthesis of trifluoromethylated 3,1-benzoxazines with a tetra-substituted stereogenic center has appeared. Only a handful of corresponding compounds are registered in the SciFinder®.[8,15] Moreover, this strategy applies to the synthesis of a variety of tetra-substituted 3,1-benzoxazines, including perfluoroalkyl and non-fluorinated derivatives, in high yields.

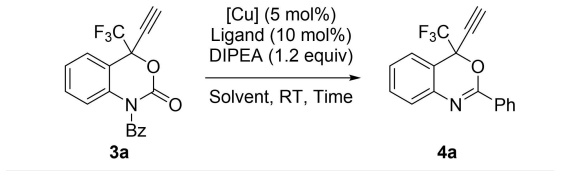
We initiated our investigation with the reaction of 4-vinyl 4-trifluoromethyl benzoxazinone **1a** under $Pd(PPh_3)_4$ catalyst in CH_2Cl_2. As expected, decarboxylative intramolecular cyclization proceeded to furnish tetra-substituted 3,1-benzoxazine **2a** in 99% yield (Table 1, entry 1). Prompted by this result, we optimized the reaction conditions by examining the effect of ligand and solvent. Another monodentate ligand, PCy_3, provided only a trace amount of **2a** after 20 h (entry 2). Although bidentate phosphine ligands such as DPEPhos and dppe also gave product **2a** in high yield, a prolonged reaction time was required (entries 3–4). Thus, with the optimal $Pd(PPh_3)_4$ catalyst, we screened solvents (entries 5–7). Even though other solvents such as toluene, THF, or DMF allowed the reaction to successfully proceed, CH_2Cl_2 gave the best result.

With the optimal conditions in hand, the substrate generality of the Pd-catalyzed decarboxylative cyclization was examined using a broad array of substituted *N*-benzoyl benzoxazinones **1a**–**o** (Scheme 2). As shown in Scheme 2, a range of *N*-benzoyl benzoxazinones containing both electron-donating and electron-withdrawing groups on the benzene rings furnished the desired tetra-substituted 3,1-benzoxazines **2** quickly in high yields. Benzoxazinone **1b** with an electron-donating alkyl group on benzoyl gave **2b** in 92% yield. Even with halogen-substitution, including of the extremely electronegative fluorine atom, on the benzoyl group, the reaction proceeded efficiently to furnish high yields regardless of the *ortho*-, *meta*, or *para*-position (**2c**: 86%; **2d**: 90%; **2e**: 86%). Furthermore, the hetero-aryl ring and π-extended naphthyl substitution were tolerated in this reaction (**2f**: 96%; **2g**: 91%). We further explored the effect of substitution on the benzene rings of benzoxazinones. Regardless the electronic nature and substitution position, the desired products were successfully obtained with a benzoyl group (**2h**: 99%; **2i**: 96%; **2j**: 95%; **2k**: 80%) and a 4-*t*Bu-benzoyl group (**2l**: 98%; **2m**: 86%; **2n**: 83%). It is noteworthy that 4-vinyl 4-pentafluoroethyl benzoxazinone **1o** also underwent the reaction to provide **2o** in 40% yield when heated.

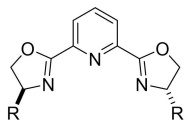


Scheme 2. The substrate scope of tetra-substituted vinyl 3,1-benzoxazines. Isolated yield values are shown. (a) 40 °C and 1.5 h.

Table 2. Optimization of reaction conditions for ethynyl-benzoxazinones.[a]



Ligand

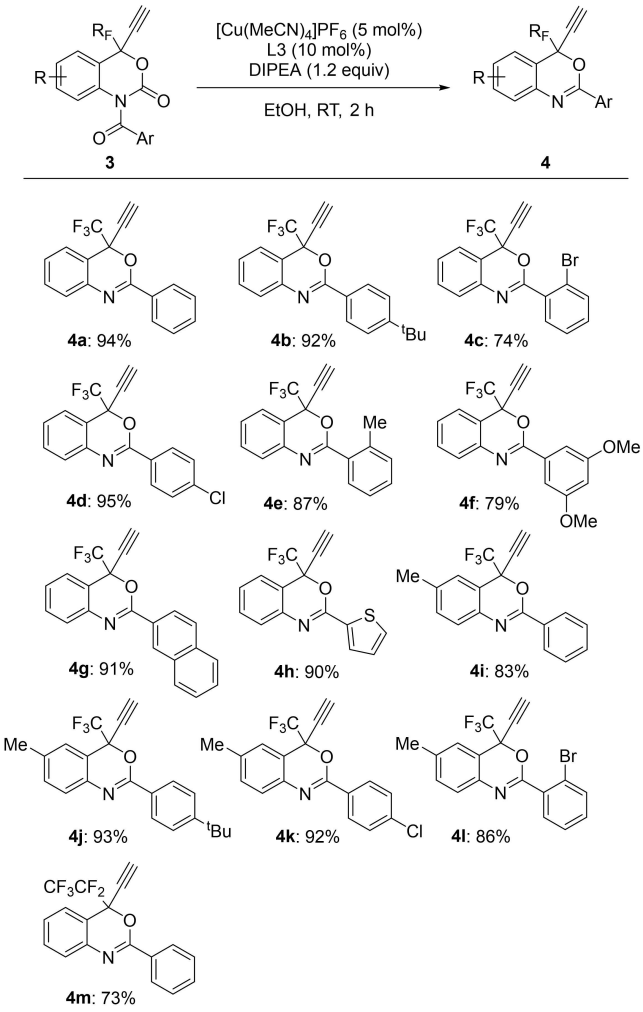


Entry	[Cu]	Ligand	Solvent	Time/h	Yield/%[b]
1	$[Cu(MeCN)_4]PF_6$	L1	MeOH	2	72
2	$[Cu(MeCN)_4]PF_6$	L2	MeOH	19	11
3	$[Cu(MeCN)_4]PF_6$	L3	MeOH	2	86
4	$Cu(OTf)_2$	L3	MeOH	2	76
5	$[Cu(MeCN)_4]PF_6$	L3	EtOH	2	94
6	$[Cu(MeCN)_4]PF_6$	L3	MeCN	2	84
7	$[Cu(MeCN)_4]PF_6$	L3	THF	18	89
8	$[Cu(MeCN)_4]PF_6$	L3	CH_2Cl_2	18	88

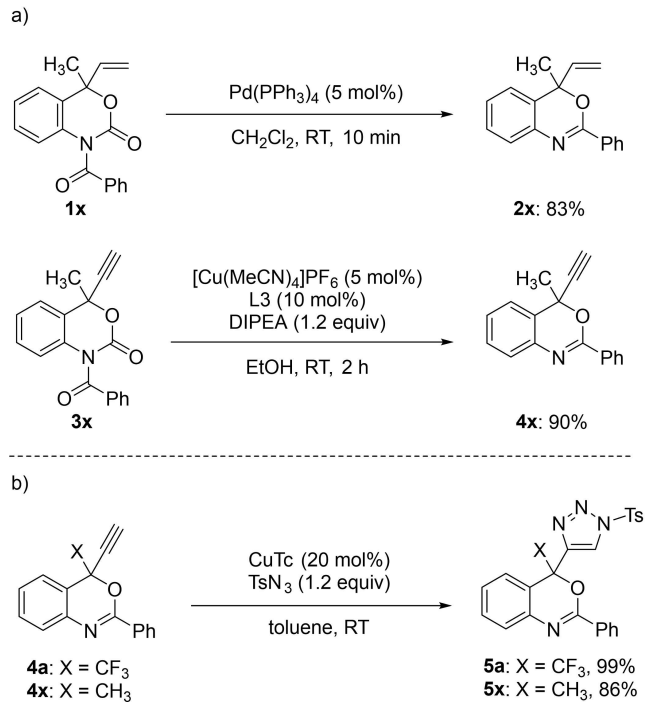
[a] Reaction was carried out with **3a** (0.05 mmol), [Cu] (5 mol%), ligand (racemic, 10 mol%), DIPEA (1.2 equiv) in solvent (1.0 mL) at room temperature. [b] Determined by ^{19}F NMR in crude using $PhCF_3$ as an internal standard.

Next, we attempted to expand this transformation to the Cu-catalyzed decarboxylative intramolecular cyclization of 4-ethynyl 4-trifluoromethyl benzoxazinone **3a** (Table 2). As a result, the reaction with **3a**, $[Cu(MeCN)_4]PF_6$ catalyst and *rac-i*Pr-PyBOX ligand in MeOH solvent allowed decarboxylation to proceed followed by an intramolecular C_1-attack to afford tetra-substituted 3,1-benzoxazine **4a** in 72% yield (entry 1). Encouraged by this initial result, we investigated the optimization of reaction conditions. While the *rac-t*Bu-PyBOX ligand resulted in low yield, *rac*-Ph-PyBOX increased yield to 86% (entries 2–3). A copper(II) catalyst, $Cu(OTf)_2$, gave lower yield (76%, entry 4). After solvent screening with the optimal catalyst (entries 5–8), the reaction proceeded efficiently with EtOH to furnish 94% yield.

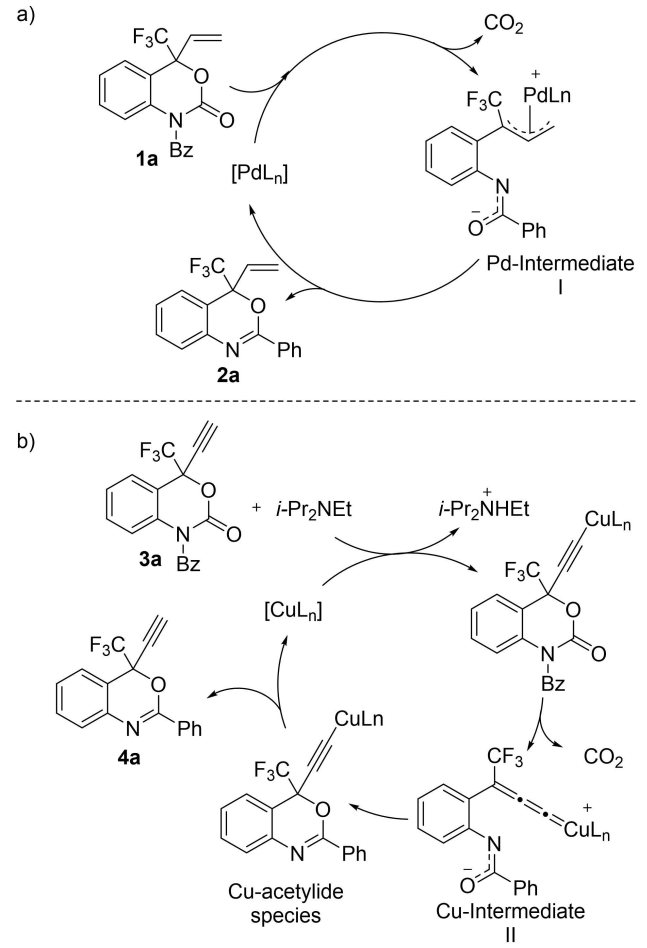
Subsequently, we examined the substrate scope using a range of substituted 4-ethynyl 4-trifluoromethyl benzoxazinones, **3a**–**3l**, with varying substitution patterns of benzene rings (Scheme 3). The desired trifluoromethyl-ethynyl-3,1-benzoxazines **4a**–**4l** were obtained in good yield, regardless of the substitution effects. The electron-donating groups at *para*-, *ortho*-, and *meta*-positions were tolerated in this reaction to



Scheme 3. The substrate scope of tetra-substituted ethynyl 3,1-benzoxazines. Yield values shown are for isolated.



Scheme 4. a) Synthesis of non-fluorinated derivatives. b) Derivatization of products.



Scheme 5. Plausible reaction mechanisms.

give **4b**, **4e**, and **4f** (92%, 87%, and 79%, respectively). The halogen substitution on the benzoyl ring also furnished the products in good to excellent yields (**4c**: 74%; **4d**: 95%). Similarly, π-extended naphthyl and hetero-aryl substituted benzoxazinones **3g**–**h** afforded **4g** in 91% yield and **4h** in 90% yield, respectively. The benzoxazinones **3i**–**l**, which have a methyl group on the phenyl ring, provided the desired products regardless of the substitution on the benzoyl group (**4i**: 83%; **4j**: 93%; **4k**: 92%; **4l**: 86%). Furthermore, 4-ethynyl 4-pentafluoroethyl benzoxazinone **3m** also underwent the reaction to give corresponding product **4m** in 73% yield.

To further investigate the potential of this method for the synthesis of tetra-substituted 3,1-benzoxazines, we attempted the reaction using **1x** and **3x** with 4-methyl substitution instead of the trifluoromethyl group (Scheme 4a). In the case of both 4-vinyl and 4-ethynyl substrates, decarboxylation followed by the C_1-attack of amide oxygen proceeded under the optimized conditions to provide the corresponding non-fluorinated methyl-3,1-benzoxazines **2x** and **4x** (83% and 90%, respectively). The obtained products **4**, tetra-substituted ethynyl 3,1-benzoxazines, were derivatized to **5** by the Huisgen cycloaddition using TsN_3 under Cu-catalysis (Scheme 4b, **5a**: 99%; **5x**: 86%).

A plausible reaction mechanism was proposed based on previous works.[10–11,13–14] As shown in Scheme 5, in both cases, the coordination of metal-catalysts caused the decarboxylation of **1a** and **3a** to form zwitterionic intermediates **I** or **II**. The less steric amide oxygen nucleophile attacks at the C_1-position via intramolecular cyclization gave tetra-substituted benzoxazines **2a** and **4a**.

In conclusion, we disclose herein that *N*-benzoyl 4-trifluoromethyl benzoxazinones are efficient synthons for constructing tetra-substituted 3,1-benzoxazines via an intramolecular cyclization reaction. Whereas *N*-tosyl protected 4-vinyl or 4-ethynyl trifluoromethyl-benzoxazinones resulted in a C_3-attack product,[13,14] *N*-benzoyl protection allowed selective C_1-attack by the amide oxygen nucleophile to generate a tetra-substituted trifluoromethyl stereogenic carbon center. The enantioselective variants of this reaction are currently being assessed in our laboratory.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Benzoxazinones · copper · decarboxylation reactions · fluorinated compounds · heterocycle derivatives · intramolecular cyclization reactions

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