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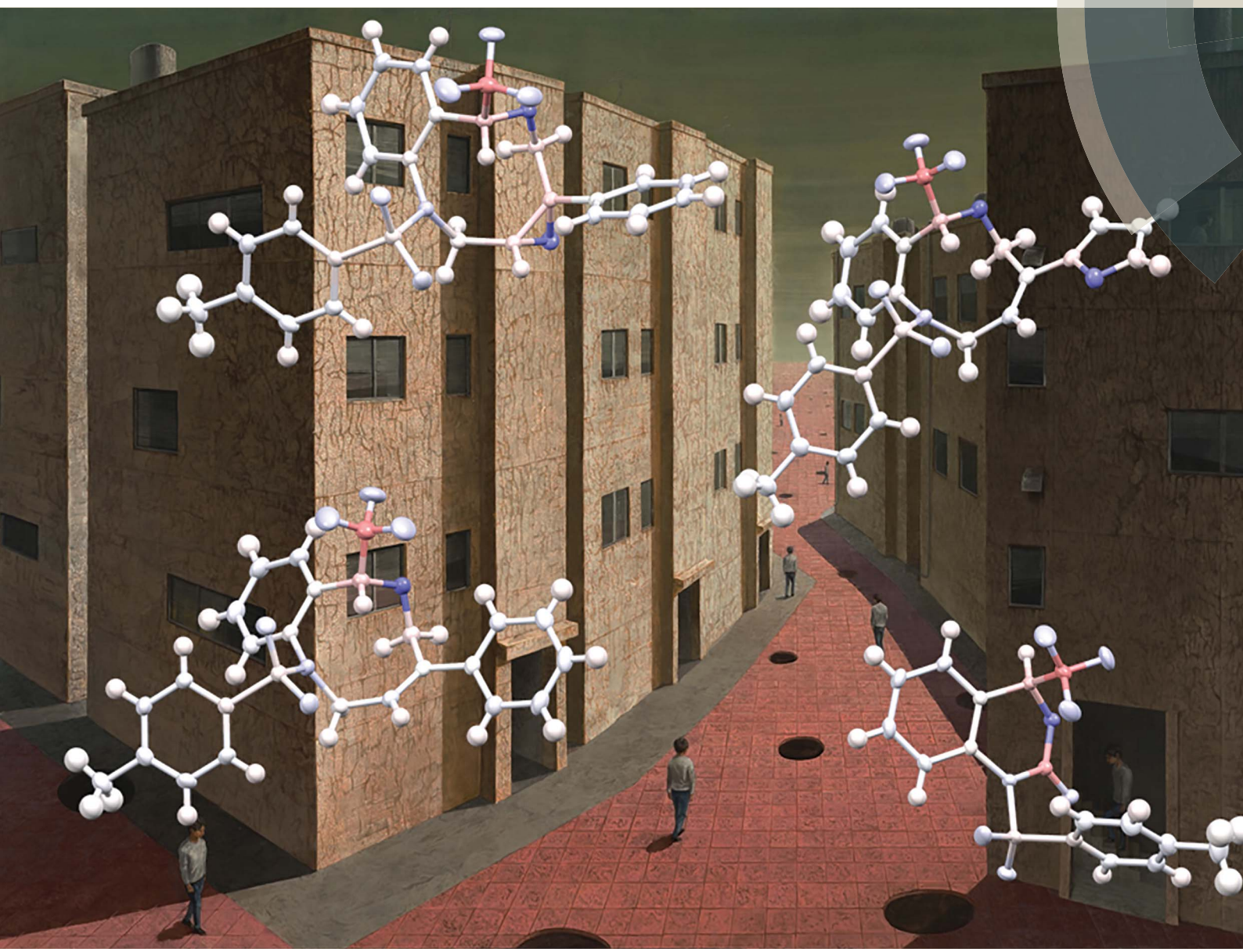

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Norio Shibata *et al.*

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Access to benzo-fused nine-membered heterocyclic alkenes with a trifluoromethyl carbinol moiety *via* a double decarboxylative formal ring-expansion process under palladium catalysis†

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Direct access to pharmaceutically attractive benzo-fused nine-membered heterocyclic alkenes **3** with a trifluoromethyl carbinol moiety was achieved *via* a palladium-catalyzed double-decarboxylative formal ring-expansion process from six-membered trifluoromethyl benzo[*d*][1,3]oxazinones **1** to nine-membered trifluoromethyl benzo[*c*][1,5]oxazonines **3** in the presence of vinylethylene carbonates **2**. Generation of a Pd-π-allyl zwitterionic intermediate was proposed in the catalytic cycle. The trifluoromethyl group in the benzoxazinanones **1** plays an important role throughout the transformation. Diastereoselective chemical transformations of products **3** were also demonstrated.

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Introduction

Fluoro-functionalized heterocycles with diverse ring sizes and ring systems have been well studied in pharmaceuticals and agrochemicals.[1] Thus, a remarkable number of publications have been dedicated to the development of efficient synthetic methods to construct fluoro-functionalized heterocycles.[1,2] In particular, heterocyclic molecules with a trifluoromethyl carbinol moiety, *i.e.*, $CF_3C(OR^1)R^2R^3$, have gathered much attention[3–6] on account of their promising biological properties. Efavirenz[4] (anti-HIV), trifluoromethylated artemisinins[5] (anti-malarial), and fluralaner[6] (insecticide and acaricide) are representative examples (Fig. 1).

In this context, our group has been engaged in the development of novel synthetic methodologies for fluorine-containing heterocycles for decades.[7] Including our reports,[7] the present synthetic strategies for fluorinated heterocyclic molecules are mostly limited to the construction of five- and six-membered ring systems,[1,2,7] while the synthesis of medium- to large-sized fluoro-functionalized heterocycles such as derivatives of benzo-oxazepine[8] and macrosphelide A[9] (Fig. 1) is extremely rare, despite the pharmaceutical importance of medium-sized heterocyclic compounds (non-fluorinated)[10] and biologically active natural products.[11] Very recently, Liu and co-workers reported an elegant method for the construction of fluoroalkyl-functionalized medium-/large-sized carbocyclic alkenes *via* an intramolecular radical trifluoromethylation–cyclization process.[12] Recently, Zhao and co-workers successfully reported the palladium-catalyzed [5 + 4] and [6 + 4] cycloaddition reactions of azadienes with vinylethylene carbonates and vinyl oxetanes respectively in good yields and selectivities.[13] We disclose herein the first synthesis of benzo-fused nine-membered heterocyclic alkenes **3** with a trifluoromethyl carbinol moiety and vinylethylene carbonates **2**[14] (Scheme 1).

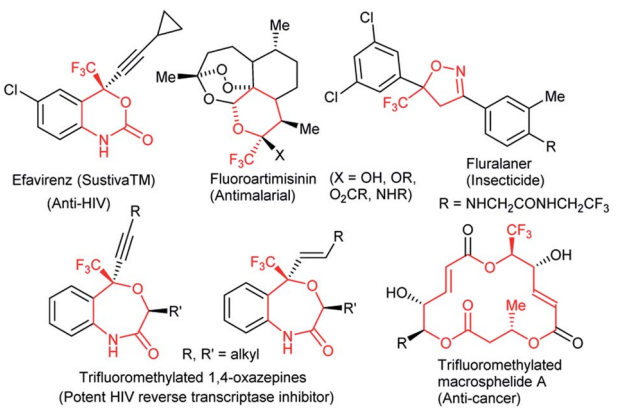

Fig. 1 Biologically active heterocycles containing a trifluoromethyl carbinol moiety.

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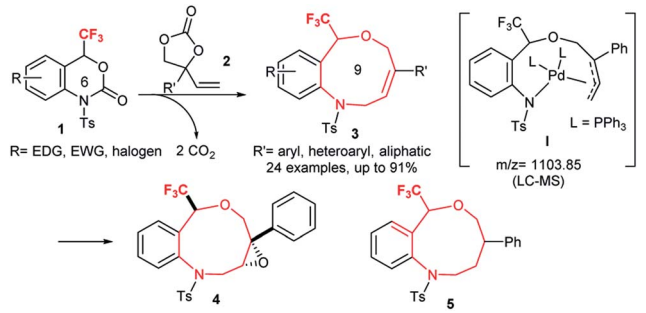


Scheme 1 Direct access to benzo-fused nine-membered heterocyclic alkenes **3** with a trifluoromethyl carbinol moiety from six-membered oxazinones **1** and vinylethylene carbonates **2** *via* palladium-catalyzed double decarboxylative cycloaddition and the further diastereoselective chemical transformations of **3**.

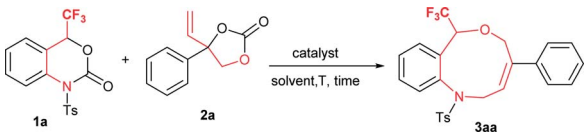
The resulting trifluoromethylated heterocycles **3** have a benzo[*c*][1,5]oxazonine skeleton, and are not only medicinally attractive fluorine-containing heterocycles,[1] but also expanded variants of well-known [1,4]oxazepine pharmaceuticals.[15] Synthesis of the titled nine-membered compounds **3** were achieved from previously unknown trifluoromethylated benzoxazinanones **1** (six-membered ring) *via* a formal ring-expansion pathway under palladium catalysis. The reaction proceeded *via* the double decarboxylation (DDC)[16] of **1** and vinylethylene carbonates **2** followed by a [5 + 4] cycloaddition reaction. The formation of Pd-complex **I** as an intermediate was proposed by LC-MS spectrometric analysis. This method provides an expedient access to trifluoromethylated benzo[*c*][1,5]oxazonines **3** with diverse functional groups in the aromatic moiety, including electron-donating, electron-deficient, and halogenic groups. Moreover, the alkene moiety in products **3** was further functionalized by conventional chemical transformations such as epoxidation to **4** and reduction to **5** (Scheme 1) with high diastereoselectivities which make this novel trifluoromethylated nine-membered skeleton more attractive as a template for drug discovery research. The presence of a trifluoromethyl group on **1** plays a pivotal role for their successful transformation to **3** based on comparative studies using non-CF_3-varients of **1**.

Results and discussion

We started a preliminary investigation with the reaction of trifluoromethyl (CF_3) benzoxazinanone **1a** and phenyl vinylethylene carbonate **2a** in the presence of suitable palladium precursors and/or phosphine ligands (Table 1). We first attempted our reaction of **1a** using similar $Pd_2(dba)_3\cdot CHCl_3$ conditions in the presence or absence of phosphine ligands, but the results were disappointing (entries 1–4). Moving on to $Pd(PPh_3)_4$ as a palladium precursor at 50 °C in THF furnished exclusively a nine-membered ring in good yield of 70% (entry 5). Motivated by this result, further optimization was carried out in different solvents. In toluene, a slight decrease in yield was observed, at 66% (entry 6), while in dichloroethane yield improved to 79% (entry 7). Lowering the temperature to room temperature (rt) furnished good yield (70%), but 40 hours were required to complete the reaction (entry 8). An excellent yield of 91% (89%) was observed by increasing the temperature to 80 °C (entry 9). Increasing the temperature further decreased yield dramatically (entry 10, see ESI for more details†).

Based on the optimized reaction conditions, the flexibility of the DDC reaction was scrutinized by using a broad array of vinylethylene carbonates (VECs) **2a–m** with **1a**. The results are summarized in Table 2. Both electron-withdrawing and electron-donating groups on the phenyl ring of **2** furnished

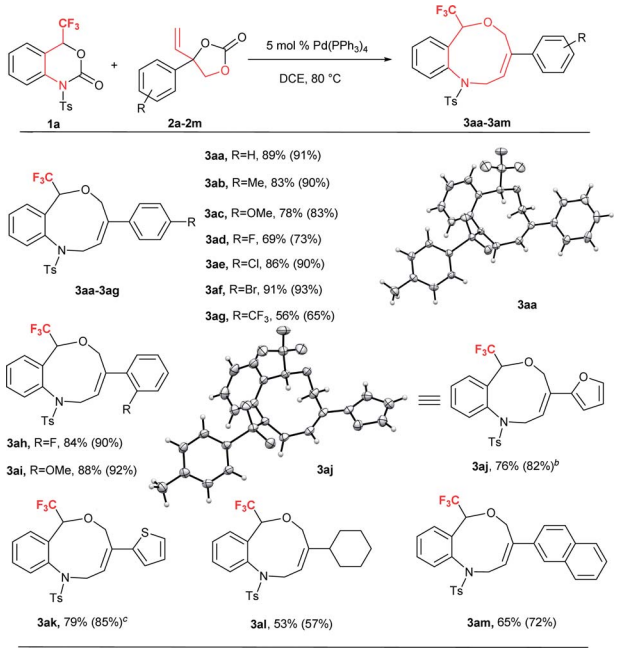
Table 1 Optimization conditions[a]



Entry	Pd catalyst (with or without ligand)	Solvent	T [°C]	t [h]	Yield[c] [%]
1[b]	10 mol% $Pd_2(dba)_3\cdot CHCl_3$	DCM	rt	24	—
2[b]	5 mol% $Pd_2(dba)_3\cdot CHCl_3$	THF	40	24	—
3	5 mol% $Pd_2(dba)_3\cdot CHCl_3$/10 mol% PCy_3	THF	40	24	—
4	5 mol% $Pd_2(dba)_3\cdot CHCl_3$/10 mol% d*t*bpmb	THF	40	24	—
5	5 mol% $Pd(PPh_3)_4$	THF	50	7	75(70)
6	5 mol% $Pd(PPh_3)_4$	Toluene	50	36	68(66)
7	5 mol% $Pd(PPh_3)_4$	DCE	50	12	83(79)
8	5 mol% $Pd(PPh_3)_4$	DCE	rt	40	79(70)
9	5 mol% $Pd(PPh_3)_4$	DCE	80	12	91(89)
10	5 mol% $Pd(PPh_3)_4$	DCE	Reflux	12	40(34)

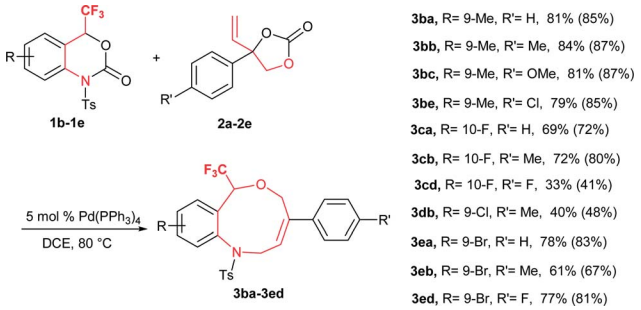
[a] Experiments were performed with **1a** (0.1 mmol), **2a** (0.15 mmol), 5 mol% $Pd(PPh_3)_4$ (0.05 mmol) in 1.0 mL solvent. [b] **2a** (0.12 mmol) was used. [c] Yields are ^{19}F NMR yields with internal standard $PhCF_3$ and yields (isolated) are also given in parentheses. d*t*bpmb = 1,2-bis(di-*tert*-butylphosphinomethyl)benzene. DCE = 1,2-dichloroethane.

Table 2 Scope of vinylethylene carbonates (VECs) 2[a]



[a] Experiments were performed with **1a** (0.1 mmol), **2a–m** (0.15 mmol), $Pd(PPh_3)_4$ (0.05 mmol) in 1.0 mL dry DCE with stirring at 80 °C for 12–16 h. Yields are isolated yields and ^{19}F NMR yields with internal standard $PhCF_3$ also shown in parentheses. **3aa**: CCDC 1575063; **3aj**: CCDC 1575065. [b] 0.20 mmol of **2j** was used. [c] 0.20 mmol of **2k** was used.

Table 3 Scope of benzoxazinanones 1[a]

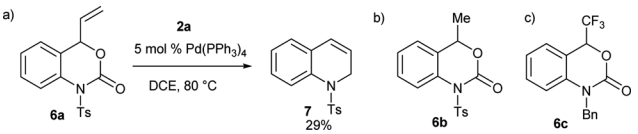


[a] Unless noted otherwise, the reaction was performed with 0.10 mmol of **1b–e** as mentioned in Table 1. Yields are isolated yields and ^{19}F NMR yields with internal standard ($PhCF_3$) also shown in parentheses.

good to excellent yields. VECs **2b–c**, which have electron-donating groups (Me and OMe) at the *p*-position, reacted efficiently to afford the desired products **3** in excellent yields (**3ab**: 83%; **3ac**: 78%) whereas VEC **2g**, which contains an electron-withdrawing group (CF_3) at the *p*-position, furnished moderate yield (**3ag**: 56%). Furthermore, halogen-substituted VECs (**2d**: F; **2e**: Cl; **2f**: Br) also underwent the DDC reaction very smoothly to furnish good to excellent yields (**3ad**: 69%; **3ae**: 86%; **3af**: 91%). Similarly, a highly electronegative atom (**2h**: F) and an electron-donating group (**2i**: OMe) at the *o*-position afforded excellent yields (**3ah**: 84% and **3ai**: 88%). Noticeably, substrates bearing an electron-withdrawing group (F) and an electron-donating group (OMe) at the *o*-position furnished higher yields than *p*-substituted substrates. Moreover, the scope of VECs **2** was extended to heteroaryl systems (**2j**: 2-furyl; **2k**: 2-thiophenyl) and the reaction proceeded smoothly to afford the desired products **3** in good yields (**3aj**: 76%; **3ak**: 79%). Gratifyingly, non-aromatic substituent VEC **2l** and extended π conjugate naphthalene-derived VEC **2m** also underwent the cycloaddition reaction to furnish **3al** and **3am** in moderate to good yield (53% and 65%, respectively), thus significantly broadening the scope of substrate **2** of this DDC system (Table 2).

Spurred by this interesting result, a range of differently substituted CF_3-benzoxazinanones **1b–e** were further examined to better understand the DDC reaction (Table 3). Substituents on **1** with electronically dissimilar properties at different positions on the benzene ring were well tolerated to provide **3** in moderate to good yields. The substrate-bearing electron-donating methyl group on the benzene ring, **1b** produced CF_3-tetrahydrobenzoxazonine **3ba** in 81% yield. The halogen-substituted CF_3-benzoxazinanones **1c** and **1e** (F and Br) produced DDC products **3** in moderate to good yields (**3ca**: 69% and **3ea**: 78%) (Table 3).

To ensure the effect of the CF_3 group at the C-4 position, next we examined the reaction of benzoxazinanones **6**, which contain different substituents at the C-4 position, with **2a** (Scheme 2). In recent years, palladium-catalyzed cyclization reactions using vinyl benzoxazinanone **6a** with a variety of substrates have been actively investigated by several groups.[17] We thus first attempted the reaction of **6a** with **2a**. Interestingly, substrate **6a** with a vinyl at the C-4 position produced a very different result. Under our best conditions, a vinyl-substituted benzoxazinanone **6a** was converted to an intramolecular cyclization product **7** in 29% yield but no desired nine-membered cyclized product was observed (Scheme 2a). We next examined the reaction using **6b** with a methyl group at the C-4 position instead, but were unable to furnish the desired product and the starting material **6b** remained (Scheme 2b). Similar no conversion was obtained when we carried out the reaction of **6c** having protected *N*-benzyl group (Scheme 2c). Although the reasons for the high reactivity of **1a** are not clear, it might be due to the higher electrophilicity value of **1a** induced by the strong electronegativity of the CF_3 group (group electronegativity of CF_3 is 3.45).[18] To ensure the effect of the CF_3 group at the C-4 position of **1a**, we performed a DFT calculation. The electrophilic value of **1a** having CF_3 at the C-4 position was estimated to be 3.67 (ω



Scheme 2 Reaction of benzoxazinanones **6a–c** which contain different substituents at the C-4 position and N-protected group, with **2a** under optimized conditions gave different results.

(eV)) while that of **5b** containing CH_3 at the C-4 position (3.33) was lower (Table S6, Fig. S1 in ESI for details†).

Interestingly, the X-ray crystallographic analysis of starting substrate **1a** revealed that **1a** has a sterically unfavourable *cis*-configuration between CF_3 and tosyl groups (Fig. 2). Although the reasons for the stabilization of **1a** in this configuration are not sure,[19] the steric repulsion might be the additional factor for the high reactivity of **1a** for decarboxylation reaction.

To demonstrate the synthetic applicability of CF_3-substituted tetrahydrobenzoxazonines **3**, epoxidation and hydrogenation reactions were carried out as displayed in Scheme 3 based on the classical work of Still and Hoveyda.[20] By using the Zhao's condition[13a] we performed the epoxidation of **3aa** in the presence of *m*-CPBA at 0 °C to rt successfully transformed to epoxide **4** with 67% yield and >20 : 1 diastereoselectivity through the peripheral attack. The X-ray crystallographic structure of **4** (CCDC 1589030†) suggested that epoxidation proceeded *via* a less hindered convex approach. Hydrogenation of **3aa** with H_2 in the presence of Pd–C at rt furnished the desired product **5** (5 : 1 dr) in 74% yield (isolated as a single isomer) (Scheme 3).

A plausible reaction mechanism of the palladium-catalyzed DDC reaction of **1a** with **2a** to **3aa** is portrayed in Scheme 4. The catalytic cycle is first initiated by the oxidative addition of Pd(0) with **2** followed by decarboxylation, which generates the π-allyl-Pd(II) complex **II**. The extremely nucleophilic nature of the alkoxide oxygen of **II** attacks the most electrophilic carbon atom attached to the CF_3 group of **1a** which triggers the opening of benzoxazinanone ring to generate reactive species **III**. Due to its highly reactive nature, species **III** immediately transforms into Pd-complex **I** *via* decarboxylation. Recently, Kleij *et al.* disclosed the similar kind of six membered Pd-complex with the

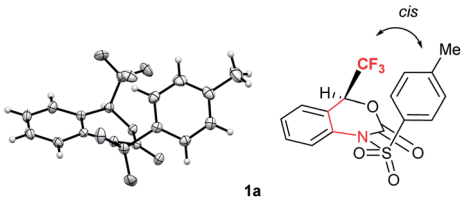
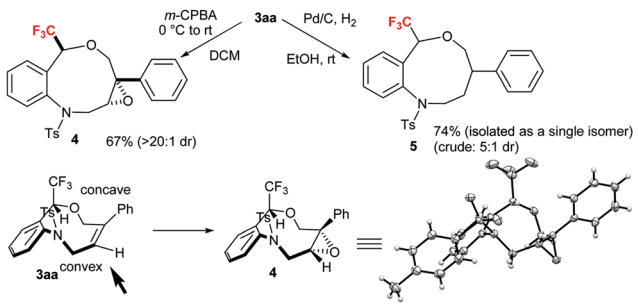
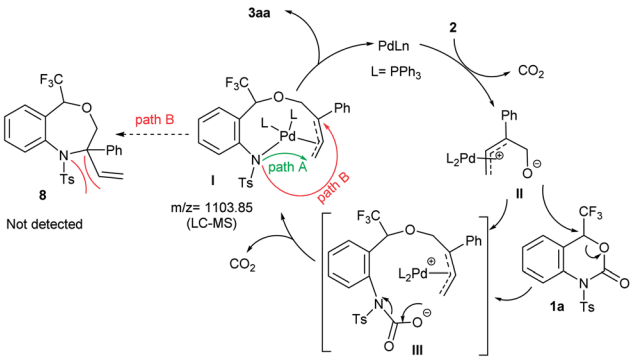


Fig. 2 X-ray crystallographic analysis of **1a** (CCDC 1575062†) revealed a sterically unfavourable *cis*-configuration between CF_3 and tosyl groups.



Scheme 3 Diastereoselective derivatizations of tetrahydrobenzoxazonine **3aa**.



Scheme 4 Plausible mechanism.

support of DFT calculations.[21] In our case, the formation of Pd-complex **I** was confirmed by LC-MS spectrometry (Fig. S2 in ESI for detail†) but we could not detect it by NMR (Fig. S3, in ESI for detail†).

From complex **I**, there might be two possible pathways for the formation of two different cyclized products. Attack at the terminal position of the Pd-complex (path A) would generate the [5 + 4] cycloaddition product **3aa** while internal attack (*i.e.*, path B) of Pd-complex could result in [4 + 3] cycloaddition to furnish a seven-membered heterocycle **8**. However, we did not obtain the [4 + 3] cycloaddition adduct **8**. This may be attributed to steric hindrance of **8**, *i.e.*, the NTs group as well as the tetra-substituted tertiary carbon center on **8**.

Conclusions

In conclusion, we have established a novel and highly efficient methodology for the synthesis of benzo-fused nine-membered heterocyclic alkenes with a trifluoromethyl carbinol moiety through a palladium-catalyzed double decarboxylative formal ring expansion process. A combination of trifluoromethylated six-membered benzoxazinanones with vinylethylene carbonates resulted in direct access to previously unknown trifluoromethyl-functionalized nine-membered heterocycles. The trifluoromethyl substituent at the C-4 position of benzoxazinanones plays an important role in this transformation. Diastereoselective transformations of the benzo-fused nine-membered heterocyclic alkene were also achieved to demonstrate the synthetic utility of the products. Investigation of the formation of other medium-sized rings as well as enantioselective variants of the reaction are presently under way in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Catalytic Transformation (ACT-C) from the JST Agency (JPMJCR12Z7).

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