Journal Name

ARTICLE

3,3-Dibromo-2-trifluoromethyl Acrylic Acid Ethyl Ester: A Versatile Platform for the Stereoselective Preparation of Functionalized- α-Trifluoromethyl α,β-Unsaturated Lactones and Trifluoromethyl Pyrazolinones

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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We herein describe a method for the synthetic routes to multi-functionalized- α-trifluoromethyl α,β-unsaturated lactones and trifluoromethyl pyrazolinones. This involves tandem stereoselective functionalization of 3,3-dibromo-2-trifluoromethyl acrylic acid ethyl ester and intramolecular cyclization reaction to afford precursors for a Suzuki-Miyaura cross-coupling reaction with arylboronic acids.

Introduction

Trifluoromethyl heterocycles have been an important motif of pharmaceutical drugs and agrochemicals because the presence of a CF_3 group can cause the improved metabolic stability, lipophilicity and bioavailability.[1] Nowadays, numerous CF_3 substituted heterocycle-containing pharmaceuticals on the market can be witnessed,[2] with examples such as trifluridine,[3] efavirenz,[4] celecoxib[5] and mefloquin.[6] Over the past decades, there has been an increasing interest in the development of method for the efficient synthesis of such fluorinated heterocyclic molecules as potential biological targets.[7] Nevertheless, synthetic method accessing an array of CF_3-containing heterocycles remains underdeveloped, in particular for nonaromatic heterocycles.[8] Considering the difficulty of introducing CF_3 moiety in nonaromatic ring systems,[9] divergent synthesis using a simple and readily available CF_3-containing precursor to convert into the diverse set of trifluoromethyl heterocyclic compounds may be one of the versatile and straightforward strategies for drug discovery.[10] In the divergent synthesis, the designing building blocks to improve compound quality and accelerate drug discovery must be chosen carefully in an early stage. In a previous paper, we disclosed an efficient synthesis of α-hydroxy-α-trifluoromethyl γ-lactams using ethyl trifluoropyruvate and enamines *via* tandem aldol condensation and cyclization reaction.[11] In addition, we developed an efficient synthesis of a series of bicycle trifluoromethyl pyrazolinone compounds using reactions of 2-aryl-3-chloro-3-trifluoromethyl acrylate.[12] Meanwhile, *gem*-dibromoalkenes have been widely used as important building blocks for organic synthesis because they act as not only coupling partners in transition-metal catalysis and also precursors of metal carbenoid intermediate formed by

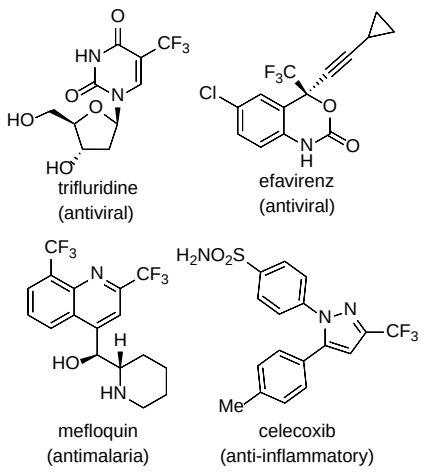

Fig. 1 Examples of trifluoromethyl heterocycle-containing drugs.

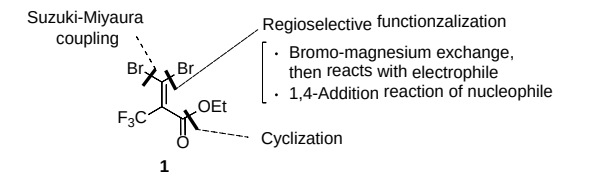

Fig 2. Our approach for synthesis of trifluoromethyl heterocycles using a novel building block, *gem*-dibromoalkene **1**.

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† Electronic Supplementary Information (ESI) available: Experimental procedures and characterization data for all novel compounds, additional crystallographic information and NMR spectra., See DOI: 10.1039/x0xx00000x

monometalation with organo-lithium and magnesium.[13] Consequently, we envisaged that trifluoropyruvate derived ethyl 3,3-dibromo-2-trifluoromethylacrylate (**1**) bearing multi-reaction sites toward regioselective functionalization (bromine-magnesium exchange and 1,4-addition reaction), cyclization and a Pd-catalyzed cross-coupling reaction might serve as a suitable precursor for

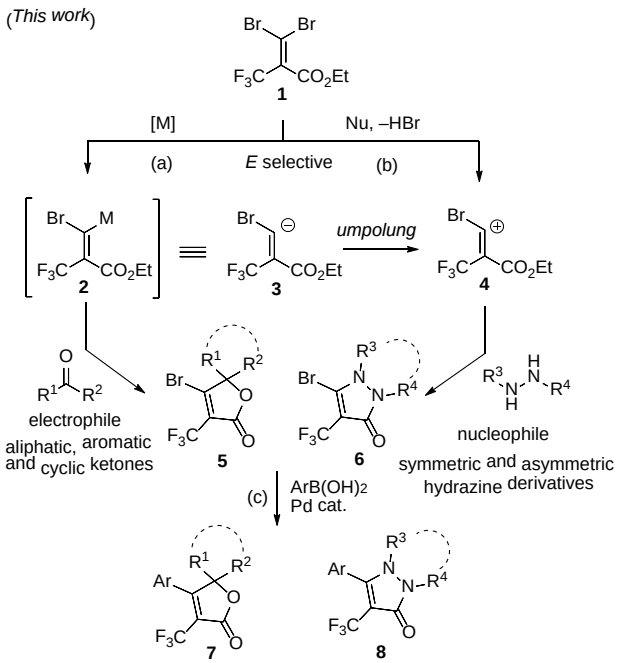


Fig 3. Approach for the diverse synthesis of multi-functionalized trifluoromethyl heterocycles.

diverse synthesis of trifluoromethyl heterocycles (Fig. 2).

Herein, we would like to report our efforts by performing two new approaches involving an umpolung strategy, with *gem*-dibromoalkene **1** as a single precursor, leading to the multi-functionalized- α-trifluoromethyl α,β-unsaturated lactones and trifluoromethyl pyrazolinones. The synthetic routes are summarized in Fig. 3: (a) a regioselective magnesium-bromine exchange reaction of **1** with organometals generates the magnesium carbenoid intermediate **2**. The intermediate **2** subsequently undergoes a tandem C-C bond formation and cyclization reaction with electrophiles such as aliphatic, aromatic and cyclic ketones, affording α-trifluoromethyl α,β-unsaturated lactones **5**. The intermediate **2** can be proposed to be an equivalent to carbanion **3**. Another way is a 1,4-addition reaction of hydrazine derivatives to *gem*-dibromoalkene **1** as Michael acceptor followed by the elimination of HBr and intramolecular cyclization to provide trifluoromethyl pyrazolinone derivatives **6** (Fig. 3:(b)). It may be said the precursor **1** is a carbocation synthon **4** which is also in a relationship with umpolung of **3**. (c) Further functionalization by using a Pd-catalyzed arylation of **5** and **6** affords the corresponding products **7** and **8**, respectively.

Results and discussion

Generation and reaction of magnesium carbenoids

To the best of our knowledge, there are few reports about the selective functionalization of fluorine-containing *gem*-dibromoalkenes. In 2004, Lu *et al*. reported that the *Z*-selective bromine-lithium exchange reaction of *O*-protected 2-trifluoromethyl-

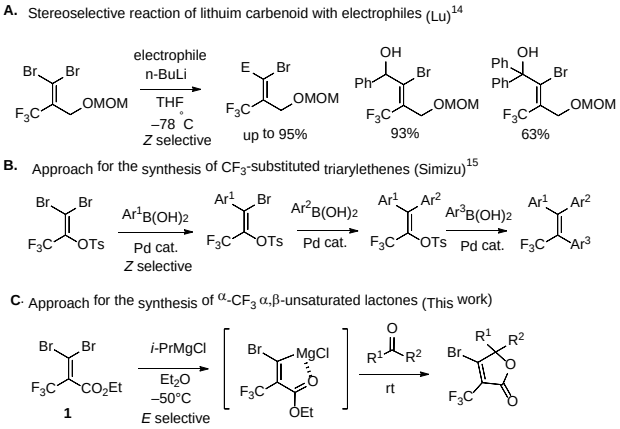
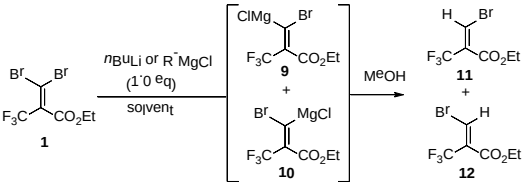


Fig. 4 Examples of novel building blocks for the regioselective functionalization.

3,3-dibromoallylic alcohol proceeded in THF under thermodynamic controlled conditions to give the corresponding carbenoid intermediate which could react with electrophiles including benzaldehyde and acetophenone, finally furnishing geometrically pure products in high yield (Fig. 4: A).[14] The stereoselectivity may be controlled by the chelation of a lithium atom with a fluorine atom. Besides, Shimizu and co-workers have engineered Pd-catalyzed stereoselective threefold cross-coupling reactions of 1,1-dibromo-3,3,3-trifluoro-2-tosyloxy-propene, in which the Pd···F interaction was proposed to account for the *Z* selectivity for the first cross-coupling process (Fig. 4: B).[15] Based on this knowledge, as reactions of fluorine-containing *gem*-dibromoalkenes usually provide *E*-products predominantly due to fluorine-metal interaction, the

Table 1. Bromine-magnesium exchange reaction of **1**



Entry	n-BuLi or RMgCl	solvent	temp. (°C)	conv. (%)[a]	**11/12**[b]
1	i-PrMgCl	THF	–80	40	60:40 (30)[c]
2	i-PrMgCl	THF	–50	93	58:42 (34)[c]
3	i-PrMgCl	Et_2O	–80	>95	27:73 (60)[c]
4	i-PrMgCl	Et_2O	–50	>95	20:80 (46)[c]
5	i-PrMgCl	hexane	–50	>95	40:60 (20)[c]
6	MeMgCl	Et_2O	–80	<5%	ND
7	n-BuLi	Et_2O	–80	<5%	ND

[a]: The conversion was determined by ^{19}F NMR analysis. [b]: The ratio was based on the relative integration ratio in ^{19}F NMR spectrum. [c]: Numbers in parenthese represent the yield base on the internal standard of benzotrifluoride.

selective reaction of bromine *trans* to the trifluoromethyl group is still challenging. In our synthetic plans, the presence of the ester of **1** was needed to aid *E* selective metal-bromine exchange due to the electrostatic interaction between the cationic magnesium and the partially negatively charged carbonyl oxygen (Fig. 4: C). The carbenoid intermediate undergoes a nucleophilic addition to a variety of ketones, followed by intramolecular cyclization accessing β-bromo-α-trifluoromethyl α,β-unsaturated lactones.

To begin our study, *gem*-dibromoalkene **1** was prepared from the reaction of 2,2,2-trifluofomethylpyruvate with carbon tetrabromide and triphenyl phosphine according to a previous report.[16] Next, some experiments were performed in order to examine the stereoselectivity and reactivity of the bromine-metal exchange reaction of **1**. When *i*-PrMgCl (1.0 equiv, 2 M in Et_2O) was added to a THF solution of **1** at –80 °C, after quenching methanol a mixture of **11** and **12** was obtained in a ratio of 1.5:1 (Entry 1, Table1). The ratio of isomers was carefully determined using ^1H and ^{19}F NMR of the crude mixtures because it was difficult to isolate products due to their volatility. The stereochemistry for **11** is determined to be in (*E*)-configuration based on the H-F coupling constant.[14,17] Next, we further investigated the impact of temperature, solvent and organometals concerning the reactivity and selectivity. The reaction with *i*-PrMgCl in THF was performed at –50 °C, and gave several unidentified by-products along with isomers **11** and **12** (*E*/*Z* = 58:42, Entry 2). When the reaction was performed at 0°C, the decomposition of **1** was observed. It should be noted that the carbenoid intermediates **9** and **10** were quite unstable. Interestingly, use of Et_2O solvent caused the opposite selectivity and improved conversion, (*Z*)-product **12** was obtained predominantly in moderate selectivity and yield (*E*/*Z* = 27:73, 60% yield). When the reaction was carried out at –50 °C, the selectively was slightly increased to E/Z = 20:80 (Entries 3 and 4). When the reaction was conducted in hexane at –50 °C instead of Et_2O, both the *E*/*Z* ratio and yield were decreased to 2:3 and 20%, respectively (Entry 5). In addition, the

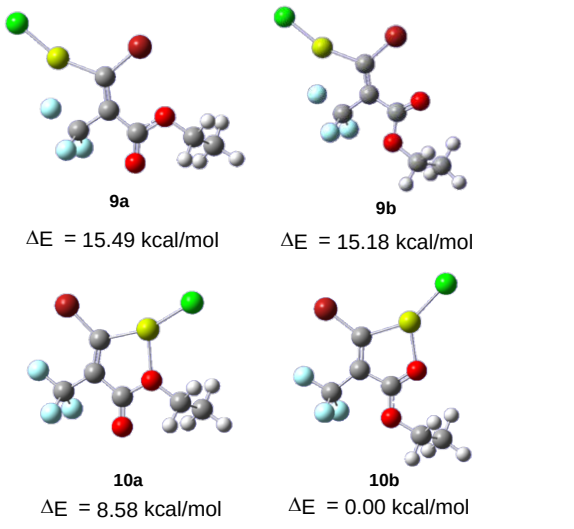
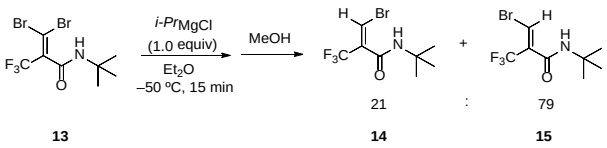


Fig. 5 Geometries and relative energies of carbenoid intermediates

treatment of **1** with MeMgCl and *n*-BuLi at –80 °C in Et_2O resulted in no conversion (Entries 6 and 7). Therefore, these results reveal that the combination of *i*-PrMgCl and Et_2O are the good choice for the generation of carbenoid **10**.

To elucidate this reaction process, we calculated the four initial geometries of the carbenoid intermediates and estimated the stability of **9** *vs.* **10** (Fig. 5).[18] The relative energies show that the geometry of the 5-membered metallacycle **10b** formed by the interaction between magnesium with carbonyl oxygen is most stable than the other geometries **9a**, **b** and **10a**. Relevant reports about the chelation of O with lithium or magnesium to control the selectivity of monometalation of dibromoalkene would support these calculated results.[19] In contract to **10b**, their relative energies reveal that **9a, b** are substantially less stable by ca.15 kcal mol^{-1}. Therefore, the transformation of **1** to carbenoid intermediate **10b** would be favorable, while the transformation to **9a, b** would be unfavorable. Nevertheless, the experimentally observed ratio was moderate (*E*/Z = 1:4, Entries 4, Table 1). We deduced from the large differential relative energies between **9** and **10** that (*E*)-**11** was the kinetic product, and no isomerisation occured. In summary, the presence of a carbonyl group of ester was crucial for (*E*)-selectivity by the coordination with magnesium. Furthermore, we assumed that the bromine-magnesium exchange reaction in Et_2O of **1** at low

Scheme 1.



temperature (–80 or –50 °C) gave the thermodynamic product **12** as the major isomer and the minor isomer **11** spontaneously. The solvent effect in detail is currently under investigation.

We further investigated the bromine-magnesium exchange reaction of 3,3-dibromo-*N*-(*tert*-butyl)-2-(trifluoromethyl)acrylamide (**13**). As shown in Scheme 1, the treatment of **13** with 1.0 equiv of *i*-PrMgCl at –50 °C in Et_2O by adding methanol after 15 min gave isomers **14** and **15** with moderate selectivity (*E*/*Z* = 21:79). The result was similar to those using **1** (Entry 4, Table1). Thus, the amide group for **13** had a minor influence on the *E*/*Z* ratio. However, we could ascertain that the chelation between carbonyl oxygen and magnesium was supposed to be the significant factor to give the regioselectivity in the bromine-magnesium exchange reaction.

With the optimum conditions in hand, we explored the reactivity of intermediate **10b** generated by the treatment of **1** with *i*-PrMgCl in Et_2O at –50 °C for 15 minutes to carbonyl substrates (Fig. 6). In the case of benzaldehyde, the reaction gave benzylalcohol by the reduction by *i*-PrMgCl. The reaction with acetophenone provided β-bromo-α-trifluoromethyl α,β-unsaturated lactone **16a** in 44% isolated yield without any the (Z)-bromine exchanged product, presumably due to concerns over the decomposition of carbenoid intermediate **9** prior to the reaction with electrophile. Therefore, we demonstrated that the carbenoid **10b** could be trapped by a series of ketones like cyclic ketone, acetophenone, 1-indanone and 3-

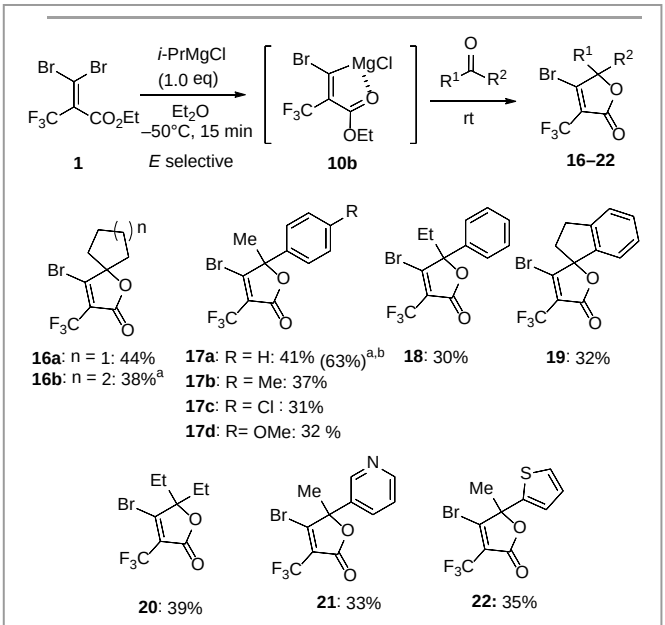


Fig. 6 Reaction of magnesium carbenoid **10b** with ketones

pentanone affording the corresponding lactones **16–20** in 30-44% yield. The transformation showed that some *para*-substituted groups of acetophenone were tolerated, including methyl, chloro and methoxy group furnishing the corresponding products **17a-d** in 31–41%. By using 2.0 equiv of **1** and i-PrMgCl to acetophenone, the isolated yield for **17a** was increased to 63% based on the carbonyl substrate. Otherwise, reactions with 3-acetylpyridine and 2-acetylthiophene gave trifluoromethyl α,β-unsaturated lactones **21** and **22** in 33% and 35% yield, respectively.

Tandem 1,4-addition-cyclization reaction of 1 with hydrazine derivatives

Previously, we disclosed that reaction of *gem*-dihaloalkene with cyclic hydrazine derivatives in 1,4-dioxane in the presence of an organic base at raised temperature could provide a variety of bicyclic pyrazolinone compounds.[12] According to the procedure, we demonstrated the further utility of **1** as novel building block for highly regioselective synthesis of 5-bromo-4-trifluoromethyl pyrazolinone derivatives. A plausible mechanism of the transformation to pyrazolinone is shown in Fig. 7. Initially, addition of either of two nitrogen atoms in hydrazine derivatives to the Michael acceptor **1** at the β position forms 1,4-adduct **28**, which undergoes regioselective elimination of HBr in the presence of *i*-Pr_2NEt, giving the corresponding acrylate intermediate **29**. Finally, the intramolecular cyclization of **29** allows for the formation of pyrazolinone ring. This tandem 1,4-addition-cycliztion reactions with some hydrazine derivative hydrobromide was amenable to give 5-bromo-4-trifluoromethyl pyrazolinones **23–27** in moderate yield with high regioselectivity. The reaction of **1** using monobenzyl hydrazine furnished the single isomer **23** in 68% isolated yield. The reaction of *N*,*N*-dimethyl hydrazine allowed for the product **24** in 63% yield. This approach allowed us to use cyclic pyrazolinone derivatives such as hexahydropyridazine and [1,3,5]oxadiazepane.

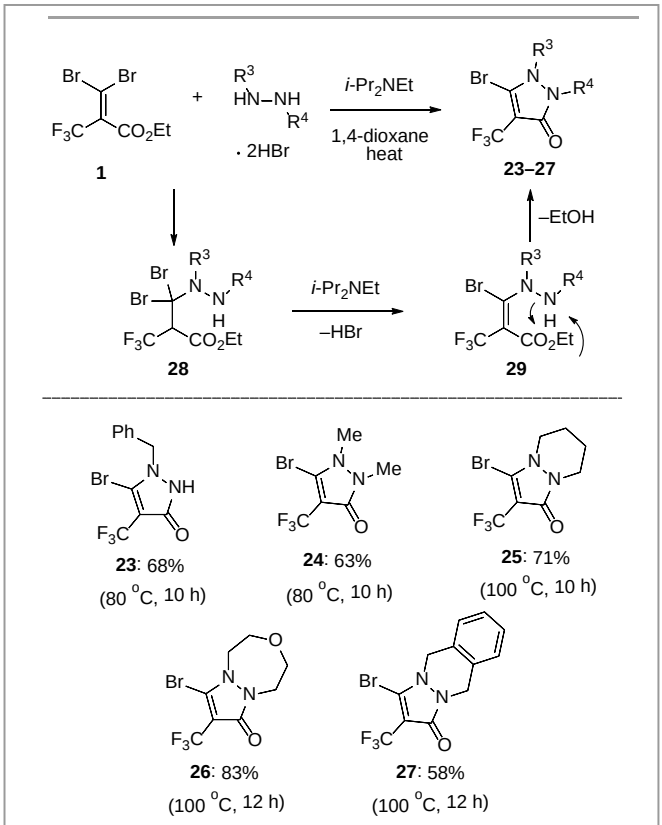


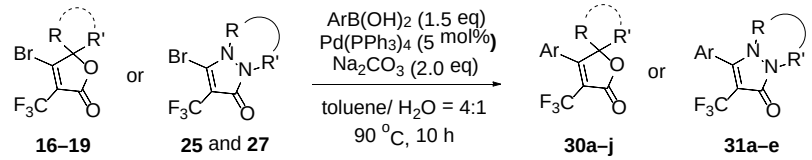
Fig. 7 Synthesis of trifluoromethyl pyrazolinones

Actually, these reactions successfully gave bicycle products **25** and **26** in 71% and 83% yield, respectively. Otherwise the reaction of 1,2,3,4-tetrahydrophthalazine provided tricyclic compound **27** in 58% yield.

Pd-catalyzed cross-coupling reactions of bromolactones and bromopyrazolinones

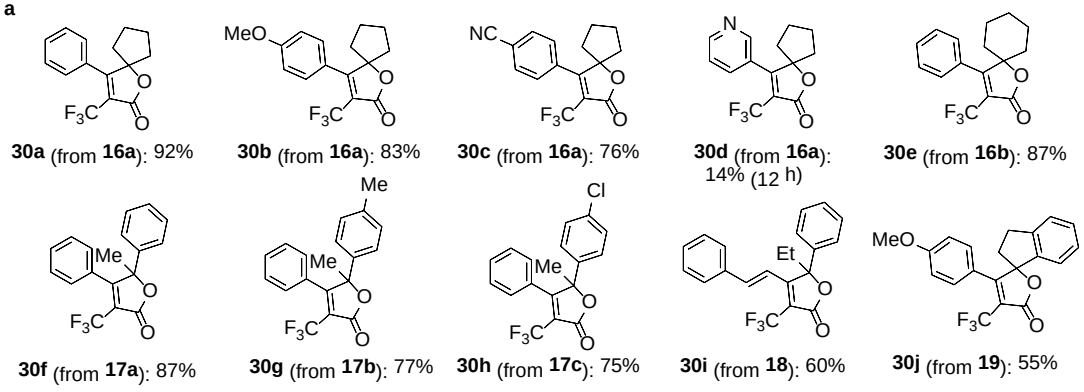
To this end, we executed further transformation of bromolactones **16-19** and bromopyrazolinone **25** and **27** by using a Suzuki-Miyaura cross-coupling reaction with various arylboronic acids (Table 2).[13a, 20] Bromolactone **16a** was chosen as a model substrate for Pd-catalyzed cross-coupling reaction. Indeed, the reaction of **16a** with phenylboronic acid in the presence of palladium (0) tetrakis(triphenylphosphine) (5 mol%) and Na_2CO_3 (2.0 eq) at 90 °C for 10 hour in a mixture of toluene and H_2O furnished the arylated product **30a** in 92% yield. Without optimization of the reaction conditions, other substrates were subject to Suzuki coupling reactions under same conditions. As illustrated in Table 2, a wide range of functional group are tolerated, including methoxy, cyano, ester and nitro group. The cross-coupling reactions with such arylboronic acids involving (*E*)-strylboronic acid were successful, and obtained the corresponding arylated products **30b,c,e–j** (55–87% yield), but 3-pyridine boronic acid resulted in poor conversion to **30d** (14% yield). Additionaly, we also performed single-crystal X-ray diffraction analysis for **30c** (Fig. 8). The structure of **30c** in solid-state shows that the geometry of 4-CN phenyl group is unequivocally *cis* to CF_3 group. In extensive experiments, we explored the reactions of bromopyrazolinones **25** and **27** with same

Table 2. Substrate scope for cross-coupling reaction with a variety of arylboronic acids.



16–19 **25** and **27** **30a–j** **31a–e**

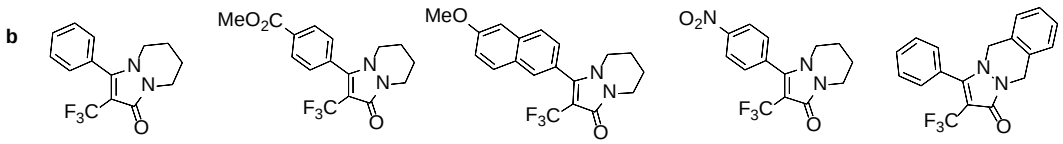
a



30a (from **16a**): 92% **30b** (from **16a**): 83% **30c** (from **16a**): 76% **30d** (from **16a**): 14% (12 h) **30e** (from **16b**): 87%

30f (from **17a**): 87% **30g** (from **17b**): 77% **30h** (from **17c**): 75% **30i** (from **18**): 60% **30j** (from **19**): 55%

b



31a (from **25**):73% **31b** (from **25**): 62% **31c** (from **25**): 77% **31d** (from **25**): 61% (22 h) **31e** (from **27**): 56%

a, Introduction of an aromatic group to bromolactones **16–19**. **b**, Pd-catalyzed cross-coupling reactions of bromopyrazolinones **25** and **27** with arylboronic acids.

conditions. Four examples of arylboronic acid were performed, an arylated pyrazolinone each **31a–e** was obtained in up to 77% yield. Use of **27** also was successful, and the reaction of **27** with $PhB(OH)_2$ proceeded smoothly to furnish the polycyclic compound

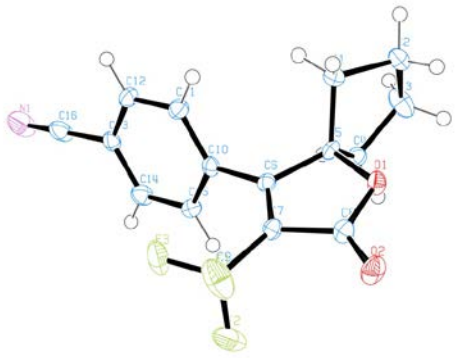


Fig. 8 ORTEP drawing of the X-ray structure of **30c**. Hydrogen atoms are omitted for clarity and ellipsoids displayed at 50% probability.

31e in 56% yield. Consequently, we were pleased to find both of bromolactones **16-19** and bromopyrazolinones **25** and **27** to be facile coupling partners for the Pd-catalyzed cross coupling reaction with various arylboronic acids.

Conclusions

In summary, we have developed a novel synthetic method accessing various multi-functionalized- α-trifluoromethyl α,β-unsaturated lactones and trifluoromethyl pyrazolinones from 3,3-dibromo-2-trifluoromethyl-acrylic acid ethyl ester **1** as a single precursor. The significant feature of our method involves two approaches: one is that a carbenoid intermediate *in situ*-generated through bromine-magnesium exchange reaction of **1**, another is a condensation of **1** with hydrazine derivatives with high stereoselectivity. Further modification of bromo- lactones and pyrazolinones by using Suzuki-coupling reactions with arylboronic acids led to a series of arylated trifluoromethyl compounds. Since α,β-unsaturated lactones and pyrazoline compounds are important part of the structure of the natural bioactive compounds,[21,22] the potential importance of these synthetic entries have stimulated our interest to develop new drugs with medicinal and agricultural applicability. The further application to evaluate their biological activity is currently underway. The detailed outcome will be reported soon.

Acknowledgements

This study was supported financially by Grants-in-Aid for Scientific Research (No. 26713041) from Japan Society for Promotion of Science (JSPS). We thank Mrs. Junko Nagaoka, of Faculty of

Engineering of Nagasaki University, for measurement of X-ray diffractometer measurements and analysis of the structure.

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