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Copper-Catalyzed Tandem C–C/C–O Bond-Forming Reactions of *ortho*-Halo-β-chlorostyrenes with Ketones: Synthesis of 4-Trifluoromethylbenzoxepines

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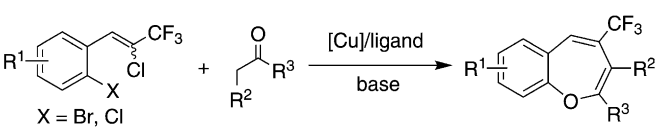
Abstract: A copper-catalyzed cyclization reaction of trifluoromethyl-containing *ortho*-halo-β-chlorostyrenes with ketones has been developed. Using a combination of copper(I) bromide, 2,2,6,6-tetramethylheptane-3,5-dione and sodium *tert*-butoxide, a variety of 4-trifluoromethylbenzoxepines was prepared in moderate to good yields by the tandem α-alkenylation of ketones with subsequent *O*-arylation.

Keywords: benzoxepines; copper; *ortho*-halo-β-chlorostyrenes; ketones; tandem reactions

Benzoxepines are an important class of heterocyclic compounds and widely represented in a variety of different biologically active molecules,[1] including natural products,[2] and natural herbicides.[3] Consequently, extensive research efforts have been focused on the development of methods for constructing the benzoxepine ring.[4] The majority of the traditional approaches available for the assembly of these molecules involve multistep transformations and harsh reaction conditions.[5] In contrast, transition metal-catalyzed cyclization reactions provide a straightforward access to these benzoxepines. For example, Lu[6] reported the synthesis of 1-benzoxepines by two cationic palladium-catalyzed [5+2] annulation reactions.[6] Ramachary et al.[7] also developed a ruthenium-catalyzed ring closing metathesis (RCM) reaction for the synthesis of highly substituted benzo[*b*]oxepines. Although the incorporation of a CF_3 group into aromatics often enhances their biological activity and has come to represent a powerful and widely used strategy in the process of drug design, to date, no synthetic methods have been reported for the synthesis of trifluoromethylated benzoxepines.[8]

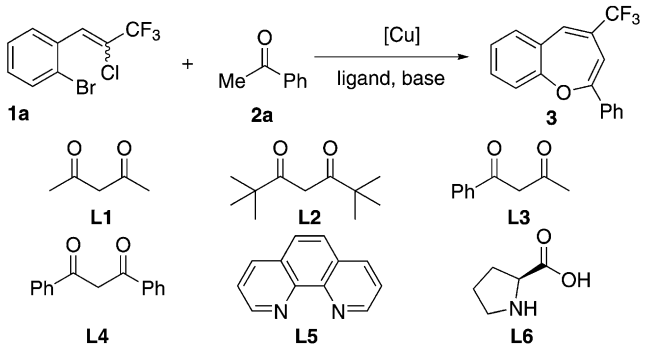
Recently, reports in the literature have highlighted the copper-catalyzed carbon-oxygen bond forming reactions.[9] The palladium-catalyzed direct α-arylation of ketones has also become a general methodology for the synthesis of α-aryl ketones.[10] A copper-catalyzed α-arylation of activated methylene compounds, including malonates[11] and β-keto esters[12] has also been developed. To the best of our knowledge, however, the copper-catalyzed α-arylation or alkenylation of simple ketones still remains a challenging area for exploration. As part of our ongoing studies towards the synthesis of trifluoromethylated aromatic compounds,[13] we have been investigating the preparation of CF_3-contanning benzoxepines from our previously reported building blocks *via* a tandem C–C/C–O bond-forming reaction. Herein, we report a simple and efficient protocol for the synthesis of 4-trifluoromethylbenzo[*b*]oxepines by the copper-catalyzed tandem α-alkenylation of ketones with a subsequent *O*-arylation reaction (Scheme 1).

The reaction of 1-bromo-2-(2-chloro-3,3,3-trifluoroprop-1-en-1-yl)benzene (**1a**)[14] with acetophenone (**2a**) was used as a model reaction to screen for the optimal reaction conditions, and the results are summarized in Table 1. Initially, treatment of substrate **1a** with acetophenone (**2a**), CuI (10 mol%), and *t*-BuONa (3 equiv.) in DMF at 100 °C afforded the desired product **3** in 56% yield (entry 1). The structure of product **3** was confirmed by an X-ray single-crystal diffraction analysis (Figure 1).[15] Inspired by some of the ligand-accelerated C–O bond-forming reactions



Scheme 1. Synthesis of 4-trifluoromethylbenzoxepines.

Table 1. Screening or the reaction conditions.[a]



Entry	[Cu]	Ligand	Base	Solvent	Temp. [°C]	Yield [%][b]
1	CuI	–	*t*-BuONa	DMF	100	56
2	CuI	**L1**	*t*-BuONa	DMF	100	57
3	CuI	**L2**	*t*-BuONa	DMF	100	78
4	CuI	**L3**	*t*-BuONa	DMF	100	68
5	CuI	**L4**	*t*-BuONa	DMF	100	71
6	CuI	**L5**	*t*-BuONa	DMF	100	67
7	CuI	**L6**	*t*-BuONa	DMF	100	65
8	CuBr	**L2**	*t*-BuONa	DMF	100	80
9	CuCl	**L2**	*t*-BuONa	DMF	100	58
10	Cu_2O	**L2**	*t*-BuONa	DMF	100	64
11	–	**L2**	*t*-BuONa	DMF	100	30
12	CuBr	**L2**	KOH	DMF	100	40
13	CuBr	**L2**	Cs_2CO_3	DMF	100	54
14	CuBr	**L2**	K_3PO_4	DMF	100	trace
15	CuBr	**L2**	K_2CO_3	DMF	100	trace
16	CuBr	**L2**	*t*-BuONa	DMSO	100	82
17	CuBr	**L2**	*t*-BuONa	NMP	100	<5
18	CuBr	**L2**	*t*-BuONa	toluene	100	0
19	CuBr	**L2**	*t*-BuONa	DMSO	80	51
20	CuBr	**L2**	*t*-BuONa	DMSO	120	70
21[c]	CuBr	**L2**	*t*-BuONa	DMSO	100	trace

[a] *Reaction conditions:* **1a** (0.2 mmol), **2a** (0.22 mmol), [Cu] (10 mol%), ligand (20 mol%) and base (3 equiv.) in solvent (2 mL) under an N_2 atmosphere for 4 h.
[b] Isolated yield.
[c] 1-bromo-2-(2-chlorovinyl)benzene was used as substrate.

reported in the literature,[16] we proceeded to investigate some bidentate ligands with the aim of increasing the yield of the reaction (entries 2–7). Pleasingly, all of the ligands promoted the tandem reaction, with 2,2,6,6-tetramethylheptane-3,5-dione (TMHD) **L2** providing the best result with a yield of 78% (entry 3). Subsequently, we proceeded to evaluate a variety of different copper catalysts to optimize the reaction conditions. CuBr was found to be superior to CuI and the other copper salts tested, including CuCl and Cu_2O (entries 8–10). It is noteworthy that a 30% yield of product was still obtained in the absence of a copper catalyst, which suggested that the *t*-BuONa probably played a key role in the transformation (entry 11). With this in mind, several different inorganic bases were evaluated. The use of other strong bases, such as KOH and Cs_2CO_3, also worked well and provided the product in moderate yields (entries 12 and 13). The use of weaker bases, however, such as K_3PO_4 and K_2CO_3 (entries 14 and 15) resulted only in the isolation of trace amounts of the product. Finally, the effect of the solvent was examined (entries 16–18). DMSO provided the best results, with the product being obtained in 82% yield (entry 16). Lower yields were observed when the reaction was conducted at 80 or 120 °C (entries 19 and 20). It is noteworthy that the trifluoromethyl group played an important role in this annulation reaction, in that only a trace amount of the product was detected when 1-bromo-2-(2-chlorovinyl)benzene was used as the substrate (entry 21). In addition, the yield of product **3** was independent of the *E*/*Z* ratio of **1a**, with the same yield being observed when either mixtures of **1a** (*Z*/*E* = 82:18)[14c] or **1a** (*Z*/*E* = 95:5)[14d] were used.

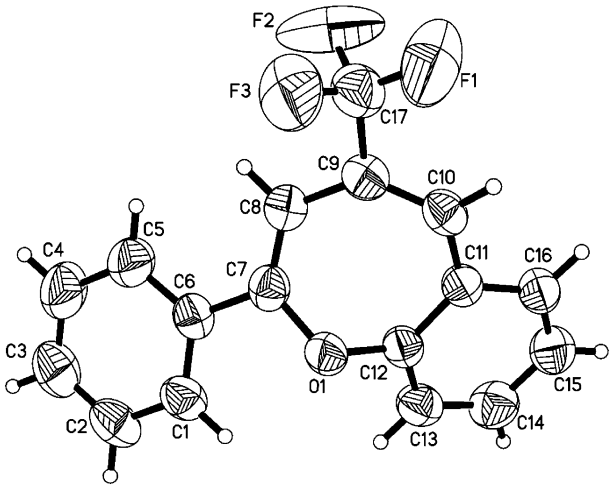
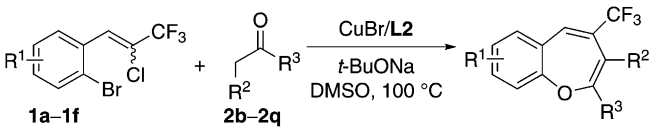
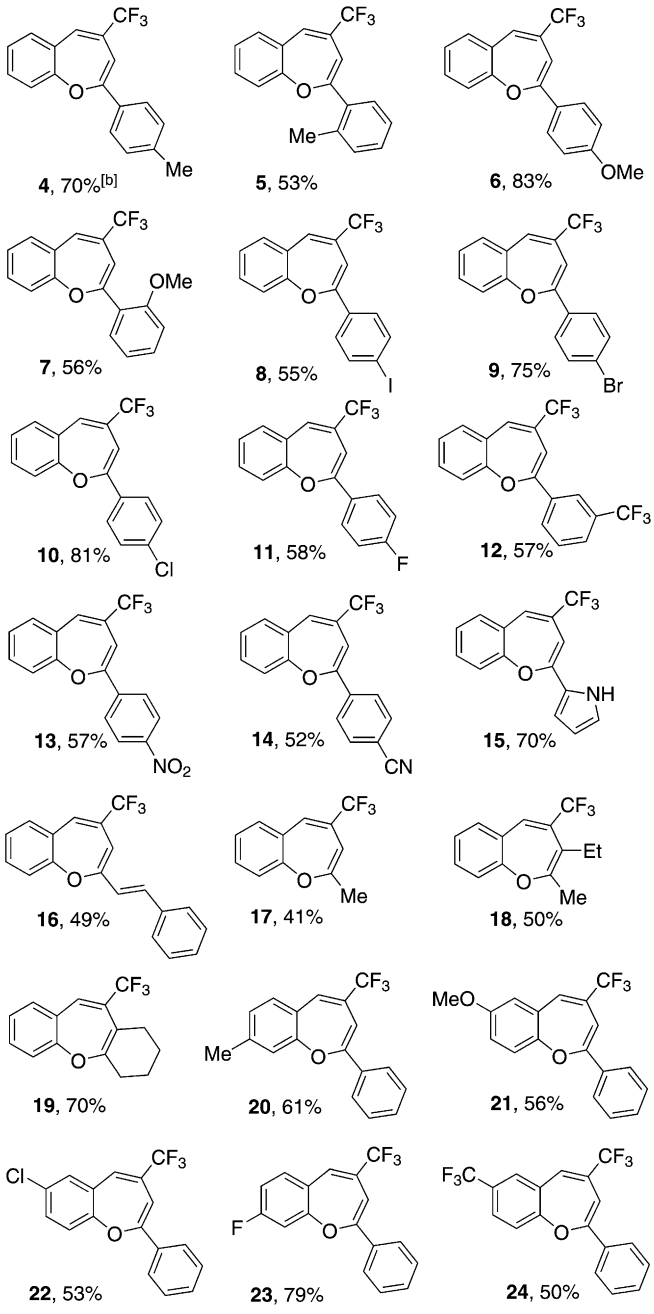


Figure 1. X-ray crystallographic structure of compound **3**

To explore the substrate scope of this tandem reaction in greater detail, a variety of different *o*-bromo-β-chlorostyrenes and ketones was examined under the standard reaction conditions (Table 2). Firstly, the reactions between ketones and substrate **1a** were evaluated in the presence of CuBr, TMHD and *t*-BuONa. The results indicated that both aromatic and aliphatic ketones were suitable substrates for the tandem reactions and could be converted successfully to the corresponding products in moderate to good yields. In general, aromatic ketones bearing electron-donation groups, such as methyl and methoxy groups, provided higher yields than those bearing electron-withdrawing group, such as CF_3, nitro and cyano groups. For example, substrates bearing a 4-methoxyphenyl or 4-nitrophenyl group underwent the tandem reaction with substrate **1a** to afford the corresponding products **6** and **13** in 83 and 57% yields, respectively. In contrast, products **5** and **7** were obtained in lower yields (53

Table 2. CuBr-catalyzed tandem reaction of *o*-bromo-β-chlorostyrenes with ketones.[a]



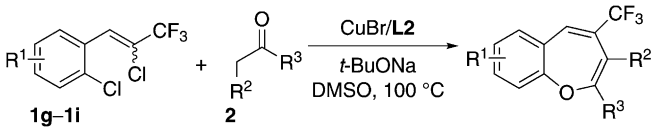


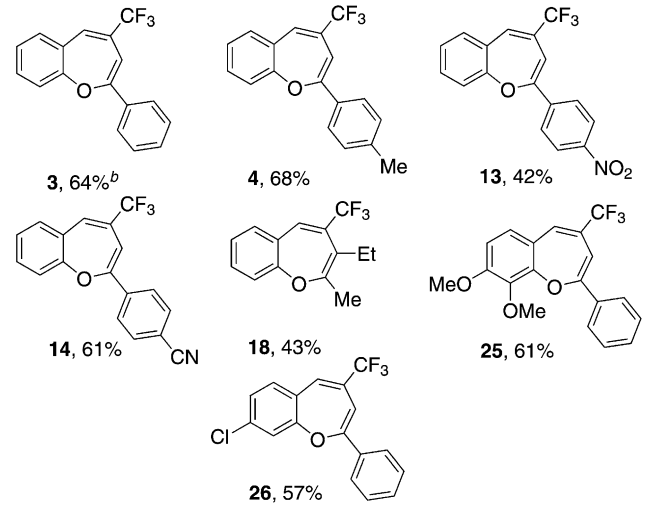
[a] *Reaction conditions:* **1** (0.2 mmol), **2** (0.22 mmol), CuBr (10 mol%), **L2** (20 mol%), and *t*-BuONa (3 equiv.) in DMSO (2 mL) at 100 °C under an N_2 atmosphere for 4 h.
[b] Isolated yield.

and 56%), presumably as a consequence of the steric hindrance provided by the *ortho*-methyl and methoxy groups. Cyclization of the *para*-halogenated acetophenones proceeded smoothly to give the corresponding products in 55–81% yields (**8**–**11**). 1-(1*H*-Pyrrol-2-yl)ethanone, which contained a heterocycle moiety, was well tolerated under the standard reaction conditions and provided product **15** in 70% yield. Similarly, aliphatic ketones were successfully subjected to the reaction conditions to provide the corresponding products **16**–**19** in moderate yields. For example, cyclohexanone reacted with **1a** under the standard conditions to provide the corresponding product **19** in 70% yield. Based on these results, we proceeded to examine a variety of *ortho*-(2-chlorovinyl)bromobenzenes bearing different functional groups on their aryl moieties. The results demonstrated that several substituents, including methyl, methoxy, chloro, fluoro, and trifluoromethyl groups, were compatible with the standard reaction conditions. For example, methyl-substituted bromobenzene was treated with acetophenone (**2a**), CuBr, TMHD and *t*-BuONa to afford the desired product **20** in 61% yield. Interestingly, a substrate bearing a fluoro group also smoothly underwent the tandem reaction with acetophenone (**2a**) to give product **23** in 79% yield.

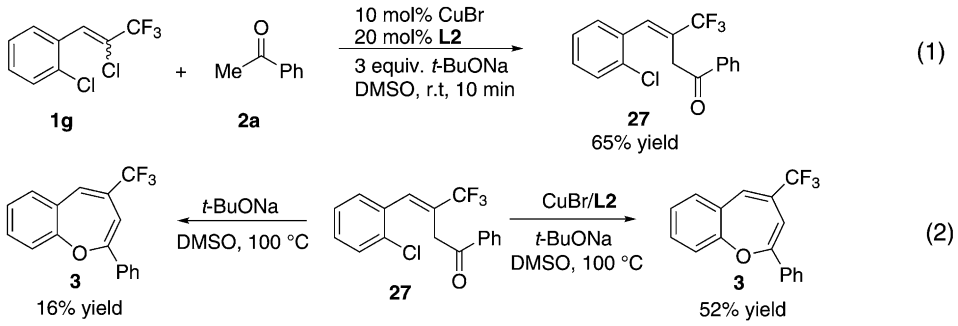
Pleasingly, the *o*-chloro-β-chlorostyrenes **1g**–**1i** were successfully subjected to this tandem reaction under

Table 3. CuBr-catalyzed tandem reaction of *o*-chloro-β-chlorostyrenes with ketones.[a]

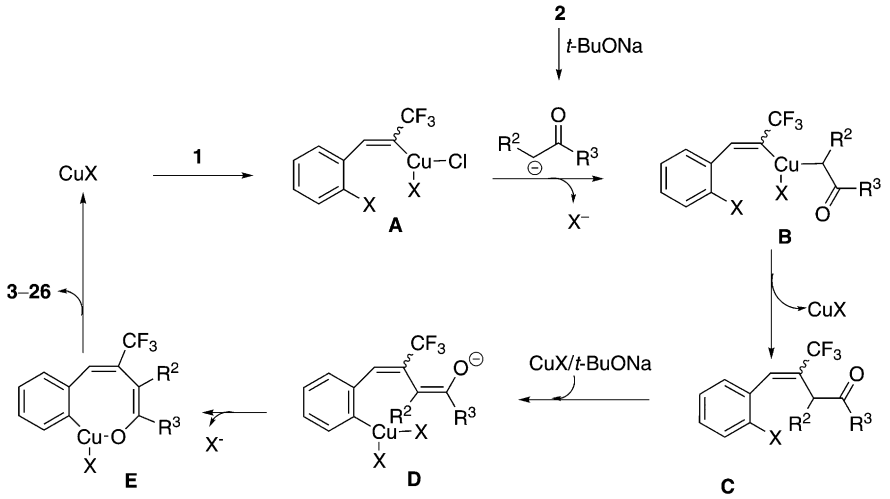




[a] *Reaction conditions:* **1** (0.2 mmol), **2** (0.22 mmol), CuBr (10 mol%), **L2** (20 mol%), and *t*-BuONa (3 equiv.) in DMSO (2 mL) at 100 °C under an N_2 atmosphere for 4 h.
[b] Isolated yield.



Scheme 2. Control experiments.



Scheme 3. Possible mechanism.

the standard reaction conditions (Table 3). The results demonstrated that the reaction between substrate **1g** and aromatic ketones containing either electron-withdrawing or electron-donating groups proceeded smoothly to give the corresponding products in 43–68% yields. For example, acetophenones bearing a 4-methylphenyl or 4-cyanophenyl group were well tolerated to provide the desired products in 68 and 61% yields. As expected, the aliphatic ketone pentan-2-one was also well tolerated by the reaction conditions and was transformed to the desired product **18** in 43% yield. Moreover, several trisubstituted chlorobenzenes were also compatible with the standard tandem reaction conditions. For instance, dimethoxy-substituted chlorobenzene reacted with acetophenone (**2a**) to afford the corresponding product **25** in 61% yield.

To elucidate the mechanism of the transformation, a control reaction was conducted between substrate **1g** and acetophenone (**2a**) in the presence of CuBr, TMHD and *t*-BuONa at room temperature for 10 min [Scheme 2, Eq. (1)]. The α-alkenylation product **27** was isolated in 65% yield. This result indicated that the α-alkenylation occurred prior to the C–O bond forming reaction under the standard conditions. Subsequent treatment of compound **27** with *t*-BuONa, CuBr and **L2** under the standard conditions provided the target product **3** in a 52% yield. In contrast, only 16% yield was obtained in the absence of copper catalyst and ligand [Eq. (2)].

Based on the present results and another mechanism reported in the literature,[10b,17] we have proposed a possible mechanism, as outlined in Scheme 3. Oxidative addition of CuX to substrate **1** would afford intermediate **A**, which could be converted to intermediate **B** following a ligand exchange process with the ketone enolate. Following a reductive elimination process, intermediate **C** could be formed with the concomitant regeneration of CuX. Subsequent keto-enol tautomerism could then occur in the presence of *t*-BuONa and the occurrence of another oxidative addition of CuX to bromobenzene or chlorobenzene would give intermediate **D**. Following the *E*/*Z*-isomerization of complex **D** at high temperature, an intramolecular ligand exchange could occur to provide copper complex **E**. Finally, reductive elimination of **E** would afford product **3**–**26** and regenerate the active CuX. A detailed study of this mechanism is in currently in progress.

In conclusion, we have successfully developed a copper-catalyzed tandem C–C/C–O bond forming reaction. In the presence of CuBr, TMHD, and *t*-BuONa, a broad range of trifluoromethyl-containing *ortho*-halo-β-chlorostyrenes underwent the cyclization reaction with ketones to give the corresponding benzo[*b*]oxepines in moderate to good yields. The annulation involved the direct α-alkenylation of ketones with a subsequent intramolecular *O*-arylation process. This protocol could be used for the synthesis of trifluoromethyl-containing building blocks, and could also provide a new strategy for the construction of benzo[*b*]oxepine rings.

Experimental Section

General Procedure for the Copper-Catalyzed Tandem C–C/C–O Bond-Forming Reaction

A flask containing a mixture of *ortho*-halo-β-chlorostyrene **1** (0.2 mmol), ketone **2** (0.22 mmol), CuBr (2.9 mg, 10 mol%), TMHD (7.4 mg, 20 mol%), *t*-BuONa (57.6 mg, 3 equiv.), in DMSO (2 mL) was evacuated and backfilled with nitrogen (3 cycles) and then the mixture was stirred at 100 °C for 4 h or until complete consumption of starting material was indicated by TLC or GC-MS analysis. After the reaction was completed, the mixture was filtered through a glass filter and washed with ethyl acetate. The mixture was washed with brine and extracted with ethyl acetate. The organic layers were dried with anhydrous Na_2SO_4 and evaporated under vacuum, and the residue was purified by flash column chromatography (hexane/ethyl acetate) to give products **3**–**26**.

2-Phenyl-4-(trifluoromethyl)benzo[*b*]oxepine (3): Yellow solid; yield: 47.1 mg (82%); mp 55.3–56.7 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.85–7.83 (m, 2H), 7.44–7.37 (m, 4H), 7.27–7.26 (m, 2H), 7.20–7.17 (m, 1H), 7.11 (d, J = 8.0 Hz, 1H), 6.33 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.2, 155.4, 134.0, 132.3, 131.2 (q, $J_{C,F}$ = 5.8 Hz), 130.1, 129.6, 129.3, 128.9 (q, $J_{C,F}$ = 30.1 Hz), 128.7, 125.8, 125.3, 123.4 (q, $J_{C,F}$ = 271.6 Hz), 121.5, 105.1 (q, $J_{C,F}$ = 2.3 Hz); ^{19}F NMR (470 MHz, $CDCl_3$): δ = −66.8 (s, 3F); IR (neat): ν = 3080, 1646, 1588, 1494, 1394, 753 cm^{-1}; LR-MS (EI, 70 eV): *m/z* (%) = 288 (M^+, 88), 105 (100), 186 (22), 165 (7), 77 (29); HR-MS (ESI): *m/z* = 289.0829, calcd. for $C_{17}H_{12}F_3O^+$ ($[M+H]^+$): 289.0835.

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[15] CCDC 906099 contains the supplementary crystallographic data for compound **3**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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