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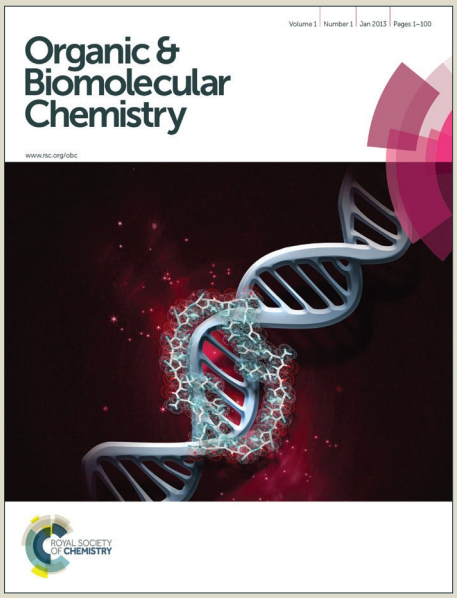

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Cu(I)-Catalyzed Oxidative Homo-Coupling of Thiazoline-4-Carboxylates: Synthesis of 4,4'-Bithiazoline Derivatives

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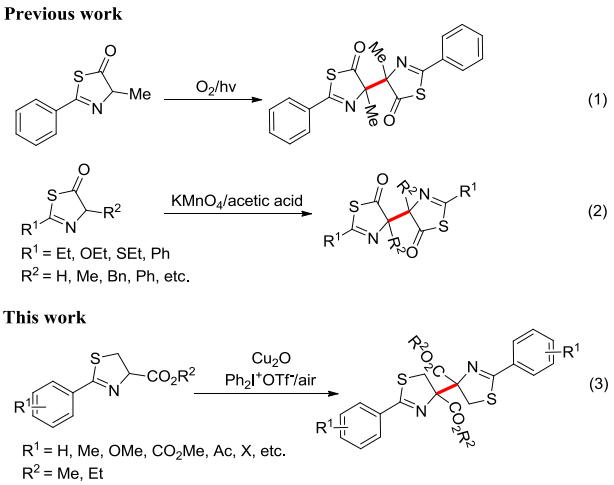
The Cu(I)-catalyzed oxidative homo-coupling of thiazoline-4-carboxylates with good functional group tolerance has been developed. The methodology presented an efficient method to directly construct vicinal carbon-hetero quaternary centers existing in numerous functional molecules and could apply to the synthesis of 4,4'-bithiazoles which are difficult to be prepared by direct C–H activation.

Dehydrogenative coupling is an efficient tool to rapidly construct C-C bonds, which satisfies the requirement of atom economy, environment protection and avoids prefunctionalized starting materials as well as unwanted stoichiometric amounts of chemical waste.[1] Among those, the homo-coupling of tertiary carbon, which involves a radical coupling sequence, is particular suitable for the building of vicinal quaternary centers attributing to the strong tendency of radical to form C-C bond and the sterically favourable effect of the coupling reaction.[2] The oxidative coupling of tertiary carbon represents one of the most straightforward methods to synthesize this kind of compounds. Many catalytic systems have been developed including Co(I),[2a] V_2O_5,[2b] CAN/aqueous KOH,[2c, 2d] and KO^{t}Bu/I_2.[2e] 4,4'-Bithiazoline derivatives as a kind of important heterocylic compounds bearing vicinal carbon-hetero quaternary centers have broad applications in the field of medicinal chemistry and material chemistry,[3] such as yersiniabactin derivative ulbactin E, which is an antibacterial agent. However, the developed synthetic methods of 4,4'-bithiazolines are limited (Scheme 1, eq.(1)(2)).[4] Compared to noble metals, copper is inexpensive and readily available and usually used to mediate various oxidative homo-coupling.[5] To the best of our knowledge, no systematic study is reported for the copper salt catalyzed dehydrogenative homo-coupling of tertiary carbon.



Scheme 1. Recent strategies for the synthesis of 4,4'-bithiazoline.

4,4'-Bithiazole derivatives are also important nitrogen-containing heterocylic skeletons which have broad applications in the field of medicinal chemistry and ligand chemistry.[6] Current methods for building of 4,4'-bithiazole skeleton, the carbon atoms of material are required to be pre-activated or special functional materials are needed.[7] Actually, it's difficult to be functionalized on C_4-position of thiazole ring via direct C–H activation.[8] Concerning our continuing interest in the functionalization of azoles,[8f-8h,9] herein we report a Cu(I)-catalyzed homo-coupling of tertiary carbon to provide a facile approach for construction of 4,4'-bithiazolines, and the coupling products could easily generate 4,4'-bithiazoles through hydrolysis and oxidative decarboxylation progress which are difficult to be prepared by direct C–H activation.

To achieve our assumption, we chose methyl 2-phenyl-4,5-dihydrothiazole-4-carboxylate (**1a**) as model substrate to optimize reaction conditions. We screened a number of

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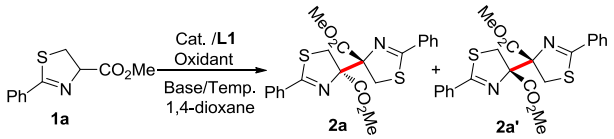
Table1. Optimization of the reaction conditions[a]

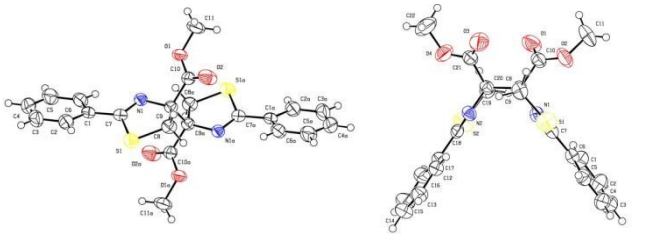


Entry	Cat. (mol%)	Oxidant	Yield (%)[b]	dr[b]
1	CuCl (10)	$Ph_2I^+OTf^-$	40	1.3:1
2	Cu_2O (10)	$Ph_2I^+OTf^-$	70	1.2:1
3	CuCN (10)	$Ph_2I^+OTf^-$	ND	/
4	$Cu(CH_3CN)_4PF_6$ (10)	$Ph_2I^+OTf^-$	40	1.9:1
5	Copper(II) 2-ethylhexanoate (10)	$Ph_2I^+OTf^-$	38	1.2:1
6	Cu_2O (10)	$Ph_2I^+BF_4^-$	67	1.2:1
7	Cu_2O (10)	$PhI(OAc)_2$	40	1.1:1
8	Cu_2O (15)	$Ph_2I^+OTf^-$	82	1.3:1
9	Cu_2O (20)	$Ph_2I^+OTf^-$	69	1.2:1
10[c]	**Cu_2O (15)**	**$Ph_2I^+OTf^-$**	**84 (86)**[d]	**1.5:1**
11[e]	Cu_2O (15)	$Ph_2I^+OTf^-$	NR	/
12	/	$Ph_2I^+OTf^-$	Trace	/
13	Cu_2O (15)	/	24	1.2:1
14[f]	Cu_2O (15)	/	Trace	/

[a] Reaction conditions: **1a** (0.4 mmol, 1.0 equiv), catalyst, **L1** (0.12 mmol), oxidant (0.08 mmol), CsOAc (0.4 mmol), 1,4-dioxane (1.0 mL), air atmosphere, 70 °C, 26 h. [b] Yield and diastereoselectivity ratio were determined by ^{1}H NMR using dibromomethane (δ = 4.80) as an internal standard. [c] 75 °C. [d] Isolated yield of two diastereoisomers. [e] Without base. [f] Under Ar atmosphere.

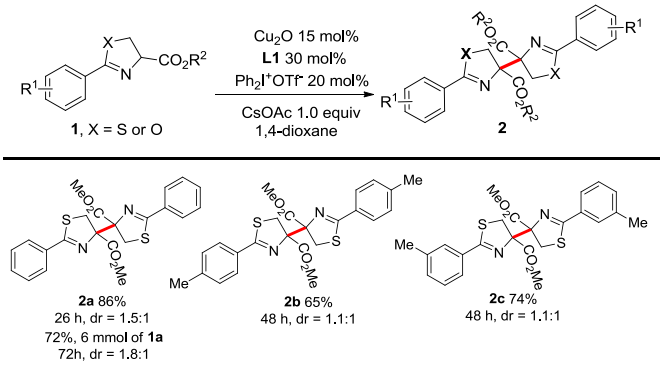
conditions including copper salts, ligands, oxidants, bases, solvents (see the Supporting Information) and some typical results were summarized in Table 1. Our initial attempt began with a catalytic amount of CuCl (10 mol%), 6-methylpicolinic acid (**L1**), $Ph_2I^+OTf^-$, 1,4-dioxane at 70 °C under air atmosphere, and the desired homo-coupling product **2a** was obtained in 40% yield with 1.3:1 dr (Table 1, entry 1). The isolated diastereoisomer structures were determined by X-ray crystal structure analysis (Figure 1).[10] Then a series of copper salts were tested, the results indicated that Cu_2O could remarkably enhance the yield to 70% (Table 1, entries 2-5). When the oxidants were replaced with $Ph_2I^+BF_4^-$ and $PhI(OAc)_2$, the yields were reduced to 67% and 40%, respectively (Table 1, entries 6-7). A yield of 82% was obtained after increasing the amount of Cu_2O to 15 mol% equivalent, while adding the catalytic loading from 10 to 20 mol% did not affect the overall outcome of the reaction (Table 1, entries 8-9). Moreover, 75 °C was found to be the best temperature for this reaction (Table 1, entry 10). Control experiments indicated that no reaction took place or only trace product was obtained in the absence of the base or catalyst (Table 1, entries 11-12). Without oxidant the yield of coupling product was decreased to 24% (Table 1, entry 13), and trace product was produced without oxidant and under argon atmosphere (Table 1, entry 14).

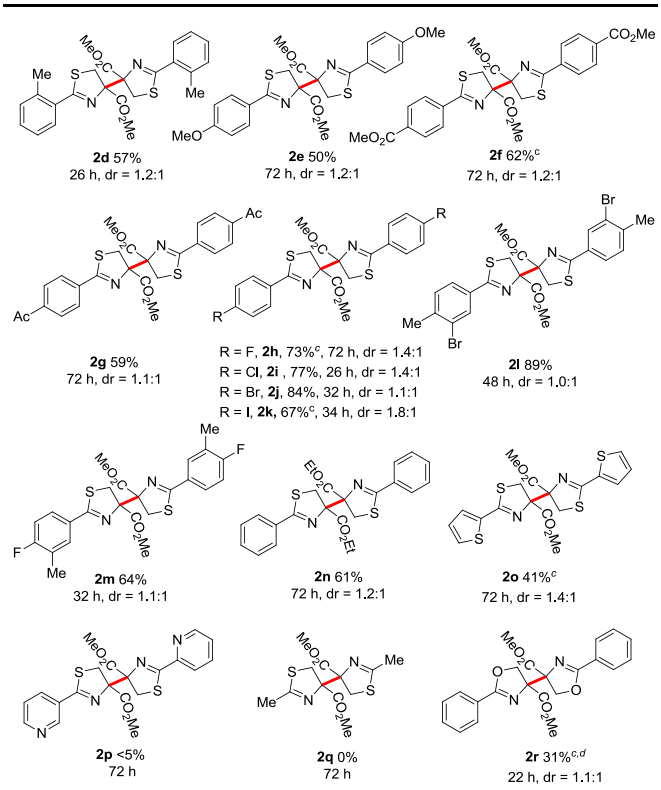
Figure 1. X-ray structures of **2a** (left) and **2a'** (right)



Based on the above optimization, the substrate scope for this Cu(I)-catalyzed oxidative homo-coupling of thiazoline-4-carboxylates was investigated (Table 2). The reaction of 4,5-dihydrothiazole-4-carboxylates (**1**) with electron-rich substituents such as methyl at *para*-/*meta*- position of phenyl ring reacted smoothly giving good to excellent yields of **2b** and **2c**. 4,5-Dihydrothiazole-substituted benzene possessing a methyl on *ortho*-position offered a relatively low yield of **2d**, which may be due to the steric effect. Strong electron-donating substituent such as methoxyl and electron-withdrawing substituents such as methoxycarbonyl and acetyl groups decreased the reaction conversion and produced moderate yields of **2e**-**2g**. The substrates bearing halogen groups (F, Cl, Br, I) on *para*-position of the phenyl ring were well tolerated, affording the corresponding **2h**-**2k** in good yields and providing synthetically useful functionalities for further transformations. Moreover, substrates possessing two substituents on the phenyl ring worked well and produced **2l** and **2m** in yield of 89% and 64%, respectively. Compared to the methyl ester derivative **2a**, ethyl ester derivative **2n** was generated in relatively low yield of 61% attributing to the steric effect. 4,5-Dihydrothiazole-4-carboxylate bearing thienyl substituent was able to furnish the corresponding product **2o** in 41% yield. However, the present system was not applicable for pyridyl and alkyl derivatives; in both cases starting substrates were recovered, while **2p** was obtained in trace and **2q** was not observed. 4,5-Dihydrooxazole-4-caboxylate was also examined, and the corresponding product **2r** was obtained with yield of 31%. In addition, when this reaction was performed on a larger scale (6 mmol, 1.33 g), **2a** could still be achieved in 72% isolated yield (958 mg).

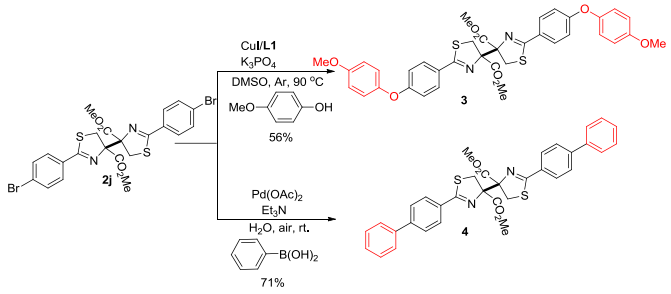
Table 2. Scope of 4,5-dihydroazole-4-carboxylates[a,b]





[a] Reaction conditions: **1** (0.4 mmol, 1.0 equiv), Cu_2O (0.06 mmol), **L1** (0.12 mmol), $Ph_2I^+OTf^-$ (0.08 mmol), CsOAc (0.4 mmol), 1,4-dioxane (1.0 mL), air atmosphere, 75 °C. [b] Isolated yields of two diastereoisomers. [c] One diastereoisomer could be isolated, diastereoselectivity ratio was determined by ^1H NMR. [d] Cs_2CO_3 was used, $Ph_2I^+OTf^-$ (0.16 mmol), 80 °C.

Scheme 2. Further transformation of 4,4'-bithiazoline-4-carboxylates



To shed light on the synthetic application of the homo-coupling products, selected 4,4'-bithiazoline was subjected to further functionalization (Scheme 2). 4,4'-Bithiazoline (R=Br, **2j**) smoothly underwent C-O coupling with *p*-methoxyphenol to furnish **3** in 56% yield.[11] In addition, **2j** with phenylboronic acid gave the corresponding C-C coupling product **4** in 71% yield.[12] Furthermore, 4,4'-bithiazoline products could be further transformed to 4,4'-bithiazole derivatives which were difficult to be prepared by direct C–H activation. First, treatment of the homo-coupling product **2** with NaOH provided hydrolysis intermediates in almost quantative yields.[13] Then 4,4'-bithiazole derivatives **5** was furnished with DDQ as oxidant in toluene at 110 °C.[14] Substrates bearing methyl on *para*-/*meta*-/*ortho*- positions or two substituents of phenyl ring were tolerated (**5b**-**5e**), and heteroaromatic ring was also suitable for this transformation (**5f**). This transformation to construct 4,4'-bithiazole derivatives could be an alternative route to this kind of derivatives.

Table 3. Scope of 4,4'-bithiazolines[a,b,c]

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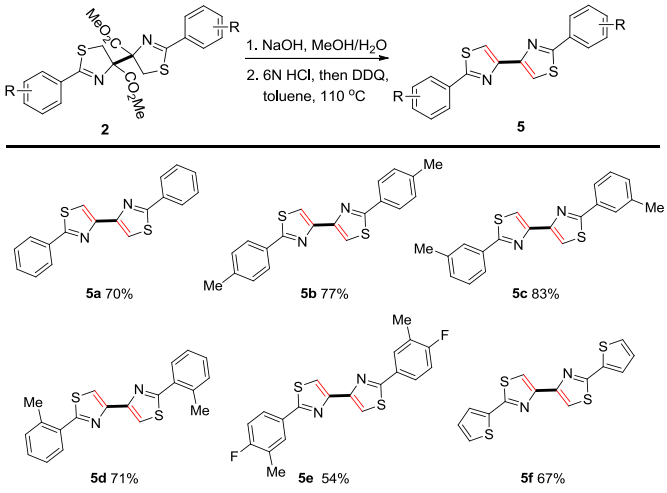
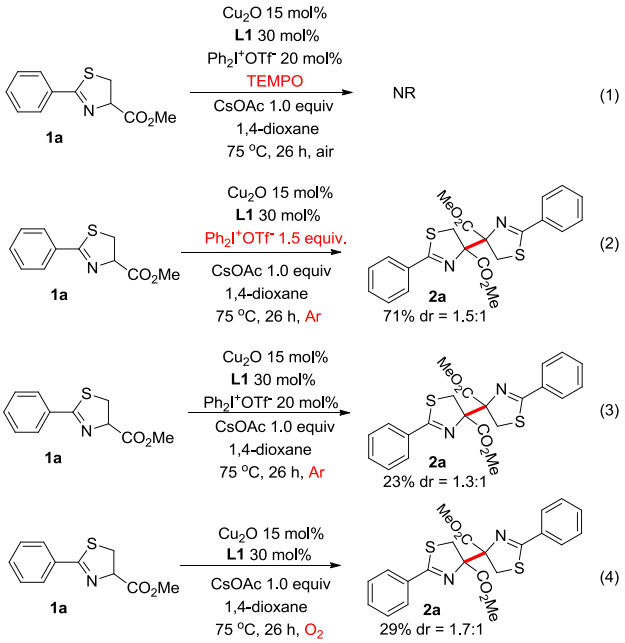


[a] Reaction conditions: (1) **2** (0.2 mmol, 1.0 equiv), NaOH (1.6 mmol), $MeOH/H_2O$ (1:1, 3.0 mL); (2) DDQ (0.6 mmol, 3.0 equiv), toluene (2.0 ml), 110 °C, 24h. [b] ^1H NMR yields using dibromomethane (δ = 4.80) as an internal standard. [c] Isolated yields.

Scheme 3. Control experiments



To gain further insights into the mechanism of the homo-coupling process, control experiments were performed (Scheme 3). When the radical scavenger TEMPO was added, no desired product was detected and starting material was recovered (Scheme 3, eq.(1)). The experimental result indicated that this coupling reaction might contain radical mechanism process. When the equivalent of $Ph_2I^+OTf^-$ was

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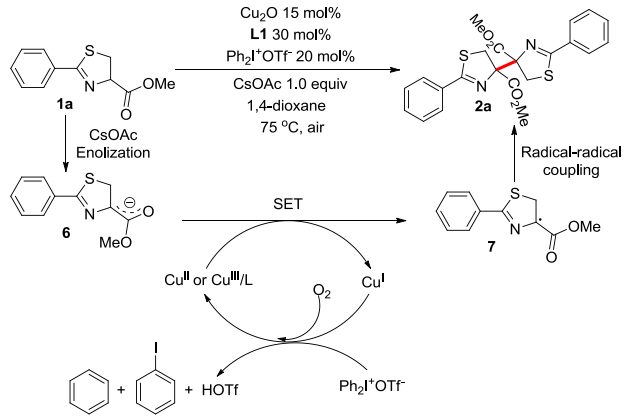
increased to 1.5 equiv. and reaction was conducted under argon atmosphere, **2a** was obtained in yield of 71%, which indicated that $Ph_2I^+OTf^-$ could be the oxidant in this coupling (Scheme 3, eq.(2)). Moreover, only 23% coupling product **2a** was obtained with the optimized condition under argon atmosphere instead of air (Scheme 3, eq.(3)). Finally, the reaction was proceeded without $Ph_2I^+OTf^-$ under argon atmosphere, **2a** was produced in yield of 29%. The two experimental results suggested that air might play a role as oxidation as same as $Ph_2I^+OTf^-$.

Based on the control experiment results and literatures,[1a, 15] the possible mechanism for this oxidative homo-coupling is proposed in Scheme 4. The first step of this transformation is enolization of **1** to afford enolate ions **6**. Meanwhile the Cu^I is oxidized *in situ* to active Cu^{II}/Cu^{III} species by $Ph_2I^+OTf^-$ and air. Subsequently enolate ions **6** further undergoes single electron transfer to provide radical **7**. Finally, radicial-radicial coupling of **7** gives the desired product **2**.

Scheme 4. Proposed mechanism of oxidative homo-coupling



In summary, we have established a practical protocol for the homo-coupling of thiazoline-4-carboxylates to construct vicinal carbon-hetero quaternary centers with a copper catalytic system. A variety of functional groups and heterocycles were tolerated. A radical-mediated mechanism was tentatively proposed. Further utilization of the method could generate functionalized 4,4'-bithiazoline-4-carboxylate derivatives and provided a facile and efficient approach for the construction of 4,4'-bithiazole derivatives by oxidative decarboxylation of homo-coupling products. Further efforts to the applications of this method are currently underway.

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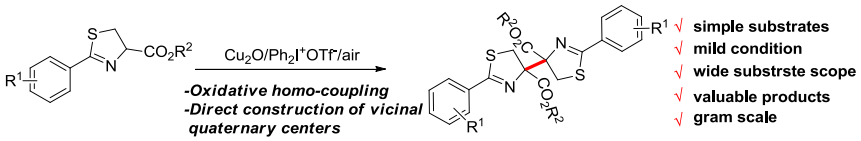

The Cu(I)-catalyzed oxidative homo-coupling of thiazoline-4-carboxylates with good functional group tolerance has been developed.