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Regio- and Stereoselective Synthesis of Multisubstituted Olefins and Conjugate Dienes by Using α-Oxo Ketene Dithioacetals as the Building Blocks

Weiwei Jin,[†] Wangming Du,[†] Qin Yang,[†] Haifeng Yu,[†] Jiping Chen,[†] and Zhengkun Yu*[,†,‡]

Dalian Institute of Chemical Physics, Chinese Academy of Sciences (CAS),
457 Zhongshan Road, Dalian, Liaoning 116023, China, and State Key Laboratory of
Organometallic Chemistry, Shanghai Institute of Organic Chemistry, CAS,
354 Fenglin Road, Shanghai 200032, China

zkyu@dicp.ac.cn

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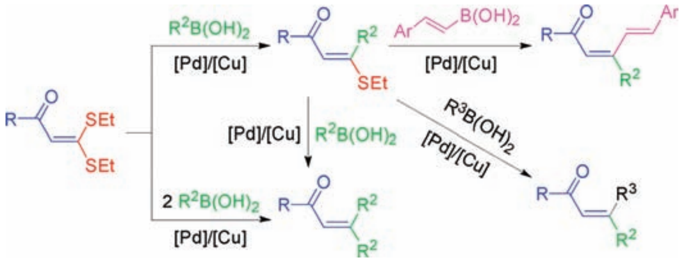
ABSTRACT



An efficient palladium(0)-catalyzed, Cu(I)-mediated synthetic route to trisubstituted olefins and conjugate dienes has been developed *via* oxo directing Liebeskind–Srogl cross-coupling reactions of *gem*-dihaloolefin-type α-oxo ketene dithioacetals with aryl and alkenylboronic acids. The synthetic protocol has demonstrated rare examples of transition-metal-promoted transformations of ketene dithioacetals, providing a novel route to highly functionalized conjugate dienes.

Efficient regio- and stereoselective construction of multisubstituted olefins, which are important structural units in many natural products, pharmaceuticals, and organic emitter materials, remains a challenge in organic synthesis.[1] Vinylboronic acids and boronates,[2] vinylzinc,[1a,2c] vinylmagnesium,[1a] vinylzirconium,[2d] and vinylaluminum[3] compounds have been used to synthesize multisubstituted olefins. *N*-directing group-bearing 2-pyridyl-vinylsilanes[4] and 2-pyrimidyl-vinylsulfides,[5] 1,1-dihaloolefins,[6] vinyl acetates[7a] and ethers,[7b] and other reagents and methods[8] have also been reported for this purpose. Catalytic C–S bond cleavage can be applied for C–C bond formation,[9]

[†] Dalian Institute of Chemical Physics.

[‡] Shanghai Institute of Organic Chemistry.

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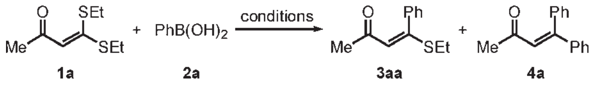
and Liebeskind–Srogl cross-coupling employing the reactions of thioesters with organic boronic acids has been well documented.[10,11] Ketene dithioacetals and 1,3-dithianes,[12] as an important class of synthetic reagents, have drawn continuous interest in the synthesis of heterocycles,[13] carbocycles, and aromatic compounds.[14] Although metal-free organic transformations of ketene dithioacetals and 1,3-dithianes have been well explored, only a few transition-metal-catalyzed systems have recently been realized in this aspect,[15,16] presumably due to easy poisoning of the dithioalkyl moieties in the dithio substrates to a transition metal catalyst. We recently reported Pd-mediated transformations of α-oxo ketene dithioacetals (**1**)[15a] and found that **1** may be used as *gem*-dihaloolefin-type vinyl building blocks. Herein, we disclose efficient Pd(0)-catalyzed, Cu(I)-mediated mono- and double arylation and alkenylation of **1** with aryl- and alkenylboronic acids (**2**) *via* oxo directing Liebeskind–Srogl cross-coupling.

Table 1. Screening of Reaction Conditions for the Cross-Coupling of α-Oxo Ketene Dithioacetal (**1a**) with Phenylboronic Acid (**2a**)[a]



(1)

entry	catalyst	[Cu]	solvent	time (h)	Yield[b] (%) (**3aa**+**4a**)[c]	**3aa**:**4a**[c,d]
1	$Pd(PPh_3)_4$		THF	14	4	100:0
2		CuTC	THF	17	6	71:29
3	$Pd(PPh_3)_4$	CuTC	THF	8[e]	93	90:10
4	$Pd(PPh_3)_4$	CuTC	THF	4[f]	100	94:6
5	$Pd(PPh_3)_4$	CuTC	THF	4[g]	100	89:11
6	**$Pd(PPh_3)_4$**	**CuTC**	**THF**	**2**	**100 (94)[h]**	**100:0**
7	$PdCl_2$	CuTC	THF	12	83	89:11
8	$Pd(OAc)_2$	CuTC	THF	12	79	73:27
9	$Pd(PPh_3)_2Cl_2$	CuTC	THF	4	100	98:2
10	$Pd(dba)_2$	CuTC	THF	12	69	81:19
11	$PdCl_2(CH_3CN)_2$	CuTC	THF	12	74	81:19
12	$Pd(PPh_3)_4$	CuI	THF	14	100 (95)[h]	99:1
13	$Pd(PPh_3)_4$	CuBr	THF	17	87	98:2
14	$Pd(PPh_3)_4$	CuCl	THF	17	95	99:1
15	$Pd(PPh_3)_4$	CuCN	THF	17	69	100:0
16	$Pd(PPh_3)_4$	Cu_2O	THF	14	5	92:8
17	$Pd(PPh_3)_4$	CuTC	toluene	4	99	99:1
18	$Pd(PPh_3)_4$	CuTC	dioxane	4	100	97:3
19	$Pd(PPh_3)_4$	CuTC	DMF	12	36	99:1
20	$Pd(PPh_3)_4$	CuTC	NMP	12	46	99:1
21	$Pd(PPh_3)_4$	CuTC	EtOH	12	54	100:0
22	$Pd(PPh_3)_4$	CuTC	THF	12[i]	89	99:1

[a] Conditions: **1a** (0.3 mmol), **2a** (0.45 mmol), catalyst (7.5 mol %), [Cu] mediator (0.6 mmol), Cs_2CO_3 (0.6 mmol), solvent (3 mL), 50 °C, 0.1 MPa N_2. [b] Yields based on **1a**. [c] Determined by GC analysis. [d] Molar ratios. [e] Without a base. [f] Using Na_2CO_3 base. [g] Using K_2CO_3 base. [h] Isolated yields of **3aa** in parentheses. [i] At 25 °C.

The reaction of α-oxo ketene dithioacetal (**1a**) with phenylboronic acid (**2a**) was initially investigated to screen the reaction conditions (Table 1). With $Pd(PPh_3)_4$ as the catalyst and Cs_2CO_3 as the base, the reaction seldom occurred in THF at 50 °C (entry 1). By means of copper(I) thiophene-2-carboxylate (CuTC)[17] as the catalyst/mediator the reaction did not efficiently proceed either (entry 2). However, under the conditions for a typical Liebeskind-Srogl cross-coupling reaction, treatment of **1a** with **2a** resulted in a 93% yield for products **3aa** and **4a** (**3aa**:**4a** = 90:10) (entry 3). Although a base is not indispensable, it obviously promoted the reaction (entries 3–6). Compound (*E*)-**3aa** was formed as the only product by ^1H NMR analysis.[18] Other Pd sources only exhibited moderate to good catalytic activity (entries 7–11). CuI also behaved as an effective mediator but exhibited a lower efficiency (entries 12–16). THF seems to be the suitable solvent for the reaction (entries 17–21). At ambient temperature, the reaction smoothly took place, selectively forming **3aa** in 89% yield (entry 22).

Under the optimized conditions, the protocol scope was explored (Table 2). The reactions of **1** with **2** predominantly or exclusively formed products of type (*E*)-**3**, suggesting a remarkable directing effect from the α-oxo group of **1**. Methyl, methoxy, *tert*-butyl, formyl, chloro, fluoro, nitro, and bromo can be tolerated as the substituents in the substrates, and the desired trisubstituted olefins **3** were obtained in good to excellent yields up to 98%. The steric

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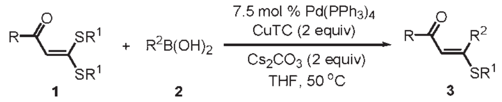
Table 2. Monoarylation and Alkenylation of **1** With Aryl- and Alkenylboronic Acids **2**[a]



(2)

entry	R, R^1 (**1**)	R^2 (**2**)	**3**	Yield[b] (%) (*E*:*Z*)[c]
1	Me, Et (**1a**)	C_6H_5 (**2a**)	**3aa**	97 (100:0)
2	Me, Et (**1a**)	2-MeC_6H_4 (**2b**)	**3ab**	65 (100:0)
3	Me, Et (**1a**)	3-MeC_6H_4 (**2c**)	**3ac**	85 (100:0)
4	Me, Et (**1a**)	4-MeC_6H_4 (**2d**)	**3ad**	92 (94:6)
5	Me, Et (**1a**)	2-MeOC_6H_4 (**2e**)	**3ae**	63 (100:0)
6	Me, Et (**1a**)	4-*t*-BuC_6H_4 (**2f**)	**3af**	84 (85:15)
7	Me, Et (**1a**)	4-CHOC_6H_4 (**2g**)	**3ag**	69 (96:4)
8	Me, Et (**1a**)	4-ClC_6H_4 (**2h**)	**3ah**	96 (100:0)
9	Me, Et (**1a**)	4-FC_6H_4 (**2i**)	**3ai**	88 (100:0)
10	Me, Et (**1a**)	3,4-$F_2C_6H_3$ (**2j**)	**3aj**	82 (96:4)
11	Me, Et (**1a**)	3,5-$F_2C_6H_3$ (**2k**)	**3ak**	73 (100:0)
12	Me, Et (**1a**)	3,4,5-$F_3C_6H_2$ (**2l**)	**3al**	62 (92:8)
13	Me, Et (**1a**)	3-$NO_2C_6H_4$ (**2m**)	**3am**	41 (100:0)
14	Me, Et (**1a**)	2-naphthyl (**2n**)	**3an**	92 (93:7)
15	Me, Et (**1a**)	*trans*-PhCH=CH (**2o**)	**3ao**	89 (88:12)
16	Me, Me (**1b**)	C_6H_5 (**2a**)	**3ba**	93 (100:0)
17	Me, Me (**1b**)	4-ClC_6H_4 (**2h**)	**3bb**	75 (100:0)
18	C_6H_5, Et (**1c**)	C_6H_5 (**2a**)	**3c**	97 (95:5)
19	C_6H_5, Me (**1d**)	C_6H_5 (**2a**)	**3d**	92 (100:0)
20	4-MeOC_6H_4, Et (**1e**)	C_6H_5 (**2a**)	**3e**	92 (100:0)
21	4-BrC_6H_4, Et (**1f**)	C_6H_5 (**2a**)	**3f**	81 (100:0)
22	*trans*-PhCH=CH, Et (**1g**)	C_6H_5 (**2a**)	**3g**	95 (81:19)
23	2-furyl, Et (**1h**)	C_6H_5 (**2a**)	**3ha**	95 (95:5)
24	2-furyl, Et (**1h**)	4-FC_6H_4 (**2i**)	**3hb**	98 (93:7)
25	2-thienyl, Et (**1i**)	C_6H_5 (**2a**)	**3ia**	91 (96:4)
26	2-thienyl, Et (**1i**)	4-FC_6H_4 (**2i**)	**3ib**	97 (91:9)

[a] Conditions: **1** (0.5 mmol), **2** (0.75 mmol), Pd(PPh$_3$)$_4$ (7.5 mol %), CuTC (1.0 mmol), Cs_2CO_3 (1.0 mmol), THF (5 mL), 50 °C, 2 h, 0.1 MPa N_2. [b] Isolated yields. [c] Molar ratios of (*E*)-**3**/(Z)-**3** determined by ^{1}H NMR analysis in $CDCl_3$.

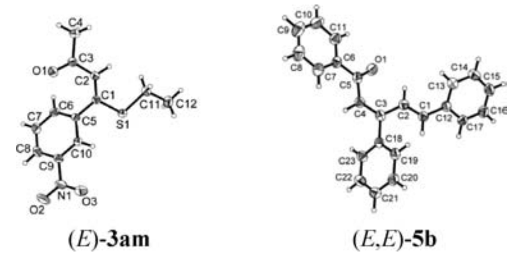
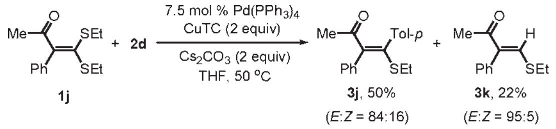


Figure 1. Crystal structures of (*E*)-**3am** and (*E*,*E*)-**5b**.

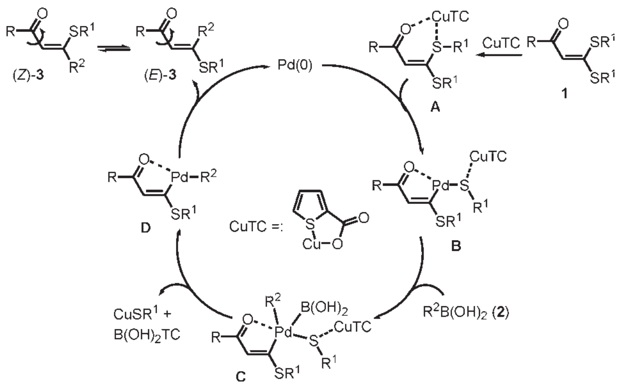
effect from *ortho*-, *meta*-, and *para*-substituents is *ortho* ≥ *meta* > *para*, and some reactions of **1a** with *para*-substituted arylboronic acids were accompanied by forming a small amount of (*Z*)-**3** isomers. 3-Nitrophenylboronic acid (**2m**) only exhibited a low reactivity, leading to trisubstituted olefin **3am** in 41% yield (entry 13). Styrylboronic acid (**2o**) reacted with **1a** afforded an 88:12 mixture of (*E*)/(*Z*)-**3ao** (entry 15). In a similar fashion, α-oxo ketene dimethyl dithioacetal (**1b**) underwent the cross-coupling reactions with **2** less efficiently than its diethyl analogue **1a**, forming the desired products in 75−93% yields (entries 16 and 17). α-Aroyl, cinnamoyl, and heteroaroyl ketene dithioacetals (**1c**−**i**) were treated with **2a** or **2i** to form the products in good to excellent yields (81−98%) with excellent stereoselectivities (entries 18−26). The (*E*)/(*Z*)-configurations of **3** were determined by ^{1}H NMR technology and confirmed by the X-ray crystallographic structural analysis of (*E*)-**3am** (Figure 1). Interconversion of (*E*)-**3** to (*Z*)-**3** isomers was observed in solution, and thus the crystals of (*Z*)-**3ha** were grown and isolated from the liquid mixture of (*E*)/(*Z*)-**3ha** (95:5) during its two-week storage at rt, and the resultant single crystal structure of (*Z*)-**3ha** was obtained.[19] Increasing the steric hindrance of **1** deteriorated formation of the desired products **3**. For example, fully substituted **1j** reacted with **2d** only afforded tetrasubstituted olefin **3j** in 50% yield as well as a reduction product **3k** (22%) (eq 3).



(3)

A reaction mechanism is proposed in Scheme 1. The Cu(I) mediator initially activates an sp^2 C−S bond positioned *cis* to the α-oxo group of **1** due to the directing functionality of the α-oxo oxygen atom by coordination to the metal center, forming species **A**. Pd(0) species is then inserted into the activated C−S bond of **A** to yield Pd(II) intermediate **B** in which the metal atom is coordinated to the α-oxo oxygen atom with formation of Pd−C and Pd−S bonds. Oxidative addition of **2** to **B** forms Pd(IV) species **C**. Reductive elimination is followed to result in product (*E*)-**3** via Pd(II) species **D** and regenerate Pd(0) species. A (*Z*)-**3** isomer may be obtained by rotation of the sp^2 ketene carbon−carbonyl carbon bond. Following the same pathway, (*E*)-**3** may undergo a Liebeskind−Srogl cross-coupling with **2** through an initial interconversion to (*Z*)-**3**.

Scheme 1. A Proposed Mechanism



Next, the protocol was applied for diarylation of **1** and further arylation and alkenylation of **3** by **2**. It was found

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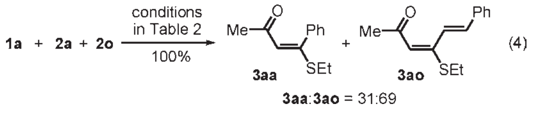
(19) The single crystal structure of (*Z*)-**3ha** was confirmed by X-ray crystallographic structural analysis. See the SI for details.

that the ligand and base effects played a crucial role in the cleavage of the second C–S bond in **1**.[20] The conditions for diarylation of **1**, arylation, and alkenylation of **3** were then optimized to $Pd(PPh_3)_4$ (7.5 mol %), dppe (7.5 mol %), CuTC (2–3 equiv), and K_2CO_3 (2–3 equiv), in THF at 50 °C for 13–24 h (see the Supporting Information (SI) for details). The diarylation products, i.e., trisubstituted olefins **4a–f**, were obtained by the one-pot double Liebeskind–Srogl cross-coupling reactions of **1** with an excessive amount of **2a** or *para*-chlorophenylboronic acid (**2h**) in 74–80% yields, respectively (Figure 2). In a similar fashion using heteroleptic (stepwise) diarylation, treatment of **3aa–c** with a variety of arylboronic acids produced the desired products **4g–p** in 63–84% yields with moderate to good stereoselectivities. Surprisingly, the reactions of **3ha** and **3ia** with **2h** exclusively afforded (*Z*)-**4q** and (*Z*)-**4r** (70–75%) as the only products, and the molecular structure of (*Z*)-**4r** was unanimously determined by X-ray crystallographic structural analysis (see the SI). With *trans*-styrylboronic acid (**2o**) as the vinylating reagent for **3**, trisubstituted conjugate dienes (*E*,*E*)-**5b–i** were exclusively formed in 69–92% yields. Such an (*E*,*E*)-configuration of **5** was verified by the X-ray crystallographic structural determination of (*E*,*E*)-**5b** (Figure 1). It was noticed that (*Z*,*E*)-**5a** was formed as the minor product, and 4-fluorostyrylboronic acid only exhibited a very low reactivity, forming (*E*,*E*)-**5j** in 11% yield.

A one-pot, two-step Liebeskind–Srogl cross-coupling strategy was tried for the synthesis of **4** and **5**, forming heteroleptic diarylation products **4j**, **5b**, and **5g** in 50–54% yields (see the SI), which has not shown any advantage over the two-pot route by applying two separate cross-coupling reactions of **1** with **2** to form **3**, and then **3** with **2** to form **4** or **5**. A competition reaction of **1a** with **2a** and **2o** (0.75 equiv each) was also carried out, affording the arylation and alkenylation products **3aa** and **3ao** in a 31:69 molar ratio (eq 4). This result suggests that alkenylation of a C–S bond in **1** is much faster than its arylation. It should be noted that olefins of type **4** may be accessed by simple aldol condensation and other methods, but it is usually difficult to get the related products of type **5** through a simple route.[2–8]



In summary, an efficient Pd(0)-catalyzed, Cu(I)-mediated regio- and stereoselective synthetic route to trisubstituted olefins and conjugate dienes has been developed by oxo directing Liebeskind–Srogl cross-coupling reactions of α-oxo ketene dithioacetals with aryl and alkenylboronic acids under mild conditions. The present methodology has demonstrated rare examples of transition-metal-catalyzed transformations of ketene dithioacetals and provided a novel route to highly functionalized conjugate dienes.

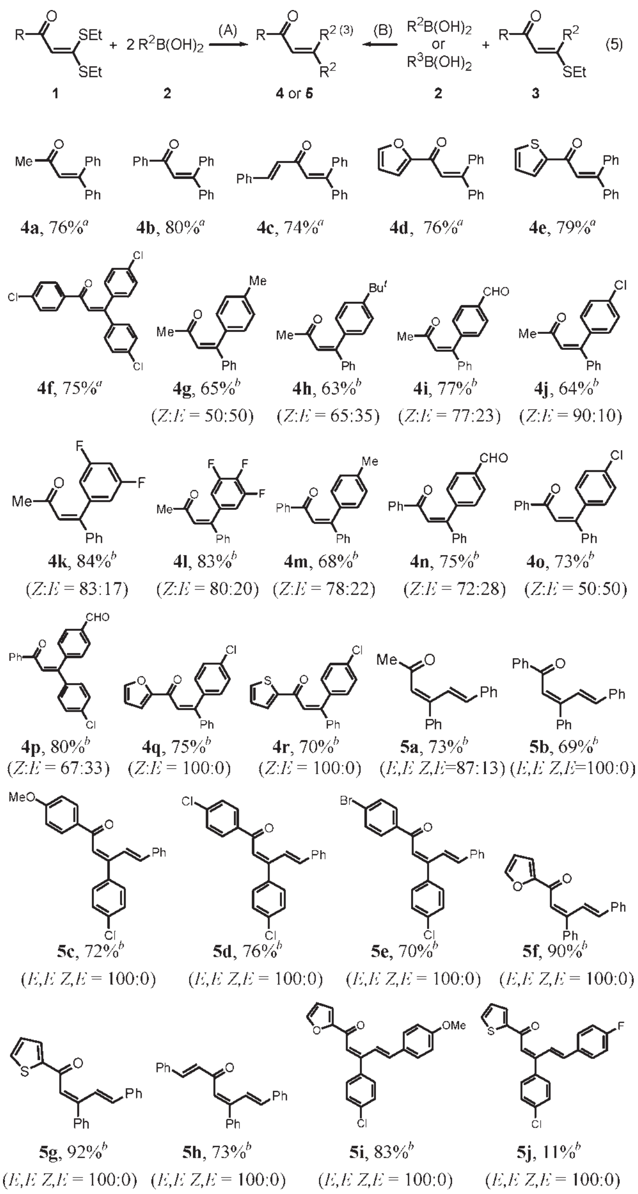


Figure 2. Cross-coupling of **1** or **3** with aryl and alkenylboronic acids **2**. Conditions: $Pd(PPh_3)_4$ (7.5 mol %), dppe (7.5 mol %), THF (5 mL), 50 °C, 13 h, 0.1 MPa N_2. Isolated yields and (*E*)/(*Z*) ratios determined by ^1H NMR analysis. [a]Conditions (A): **1** (0.5 mmol), **2** (2.0 mmol), CuTC (1.5 mmol), K_2CO_3 (1.5 mmol). [b]Conditions (B): **3** (0.5 mmol), **2** (0.75 mmol), CuTC (1.0 mmol), K_2CO_3 (1.0 mmol); for **4k**, **4l**, **4p**, and **5a–j**, 22 h.

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Supporting Information Available. Experimental procedures, analytical data and copies of NMR spectra, and X-ray crystallographic files for (*E*)-**3am**, (*Z*)-**3ha**, (*Z*)-**4r**, and (*E*,*E*)-**5b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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