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

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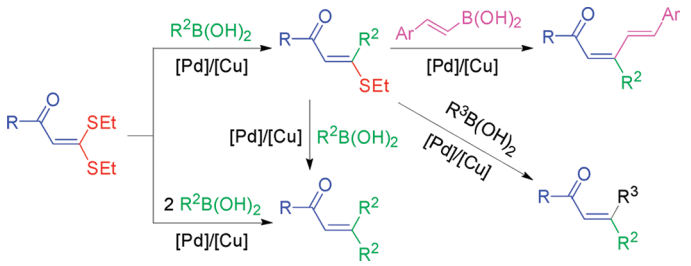
ABSTRACT



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]

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(1) (a) Bresser, T.; Knochel, P. *Angew. Chem., Int. Ed.* **2011**, *50*, 1914. (b) Feng, C.; Loh, T.-P. *J. Am. Chem. Soc.* **2010**, *132*, 17710.

(2) (a) Moquist, P. N.; Kodama, T.; Schaus, S. E. *Angew. Chem., Int. Ed.* **2010**, *49*, 7096. (b) Kerrigan, M. H.; Jeon, S.-J.; Chen, Y. K.; Salvi, L.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2009**, *131*, 8434. (c) Wang, C.; Tobrman, T.; Xu, Z. Q.; Negishi, E.-i. *Org. Lett.* **2009**, *11*, 4092. (d) Nishihara, Y.; Miyasaka, M.; Okamoto, M.; Takahashi, H.; Inoue, E.; Tanemura, K.; Takagi, K. *J. Am. Chem. Soc.* **2007**, *129*, 12634.

(3) Akiyama, K.; Gao, F.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 419.

(4) (a) Itami, K.; Ohashi, Y.; Yoshida, J.-i. *J. Org. Chem.* **2005**, *70*, 2778. (b) Itami, K.; Ushiogi, Y.; Nokami, T.; Ohashi, Y.; Yoshida, J.-i. *Org. Lett.* **2004**, *6*, 3695.

(5) (a) Muraoka, N.; Mineno, M.; Itami, K.; Yoshida, J.-i. *J. Org. Chem.* **2005**, *70*, 6933. (b) Itami, K.; Mineno, M.; Muraoka, N.; Yoshida, J.-i. *J. Am. Chem. Soc.* **2004**, *126*, 11778.

(6) For selected recent reports, see: (a) Evano, G.; Tadiparthi, K.; Couty, F. *Chem. Commun.* **2011**, *47*, 179. (b) Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2840. (c) Legrand, F.; Jouvin, K.; Evano, G. *Isr. J. Chem.* **2010**, *50*, 588. (d) Coste, A.; Karthikeyan, G.; Couty, F.; Evano, G. *Angew. Chem., Int. Ed.* **2009**, *48*, 4381. (e) Nagao, I.; Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 7573. (f) Reiser, O. *Angew. Chem., Int. Ed.* **2006**, *45*, 2838.

(7) (a) Sun, C. L.; Wang, Y.; Zhou, X.; Wu, Z. H.; Li, B. J.; Guan, B. T.; Shi, Z. J. *Chem.—Eur. J.* **2010**, *16*, 5844. (b) Nilsson, P.; Larhed, M.; Hallberg, A. *J. Am. Chem. Soc.* **2001**, *123*, 8217.

(8) (a) Barluenga, J.; Quiñones, N.; Cabal, M.-P.; Aznar, F.; Valdés, C. *Angew. Chem., Int. Ed.* **2011**, *50*, 2350. (b) Barluenga, J.; Florentino, L.; Aznar, F.; Valdés, C. *Org. Lett.* **2011**, *13*, 510. (c) Barluenga, J.; Escribano, M.; Moriel, P.; Aznar, F.; Valdés, C. *Chem.—Eur. J.* **2009**, *15*, 13291. (d) Barluenga, J.; Tomás-Gamasa, M.; Moriel, P.; Aznar, F.; Valdés, C. *Chem.—Eur. J.* **2008**, *14*, 4792.

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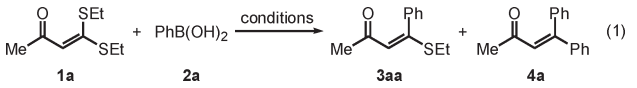
and Liebeskind–Srogl cross-coupling employing the reactions of thioesters with organic boronic acids has been well documented.[10,11] Ketene dithioacetals and 1,3-dithianes,[12] as an important class of synthetic reagents, have drawn continuous interest in the synthesis of heterocycles,[13] carbocycles, 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.

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).

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



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.

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

(9) (a) Ishizuka, K.; Seike, H.; Hatakeyama, T.; Nakamura, M. *J. Am. Chem. Soc.* **2010**, *132*, 13117. (b) Creech, G. S.; Kwon, O. *J. Am. Chem. Soc.* **2010**, *132*, 8876. (c) Kobatake, T.; Fujino, D.; Yoshida, S.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2010**, *132*, 11838.

(10) (a) Prokopcová, H.; Kappe, C. O. *Angew. Chem., Int. Ed.* **2009**, *48*, 2276. (b) Liebeskind, L. S.; Srogl, J.; Savarin, C.; Polanco, C. *Pure Appl. Chem.* **2002**, *74*, 115.

(11) For selected recent reports on Liebeskind–Srogl cross-coupling, see: (a) Liebeskind, L. S.; Yang, H.; Li, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 1417. (b) Yang, H.; Li, H.; Wittenberg, R.; Egi, M.; Huang, W. W.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2007**, *129*, 1132. (c) Zhang, Z. H.; Liebeskind, L. S. *Org. Lett.* **2006**, *8*, 4331. (d) Yu, Y.; Liebeskind, L. S. *J. Org. Chem.* **2004**, *69*, 3554. (e) Kusturin, C. L.; Liebeskind, L. S.; Neumann, W. L. *Org. Lett.* **2002**, *4*, 983. (f) Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2001**, *3*, 91. (g) Liebeskind, L. S.; Srogl, J. *J. Am. Chem. Soc.* **2000**, *122*, 11260.

(12) (a) Liu, J.; Wang, M.; Han, F.; Liu, Y. J.; Liu, Q. *J. Org. Chem.* **2009**, *74*, 5090. (b) Kobatake, T.; Yoshida, S.; Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2340. (c) Kim, H.; Park, Y.; Hong, J. Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 7577.

(13) For selected recent reports, see: (a) Li, Y. F.; Xu, X. X.; Tan, J.; Xia, C. Y.; Zhang, D. W.; Liu, Q. *J. Am. Chem. Soc.* **2011**, *133*, 1775. (b) Zhang, L. J.; Xu, X. X.; Tan, J.; Pan, L.; Xia, W. M.; Liu, Q. *Chem. Commun.* **2010**, *46*, 3357. (c) Tan, J.; Xu, X. X.; Zhang, L. J.; Li, Y. F.; Liu, Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 2868. (d) Misra, N. C.; Ila, H. *J. Org. Chem.* **2010**, *75*, 5195. (e) Kumar, S.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2009**, *74*, 7046. (f) Kumar, S.; Peruncheralathan, S.; Ila, H.; Junjappa, H. *Org. Lett.* **2008**, *10*, 965. (g) Rao, H. S. P.; Sivakumar, S. *J. Org. Chem.* **2006**, *71*, 8715.

(14) For selected recent reports, see: (a) Wang, M.; Fu, Z. Q.; Feng, H.; Dong, Y.; Liu, J.; Liu, Q. *Chem. Commun.* **2010**, *46*, 9061. (b) Hu, J. L.; Zhang, Q.; Yuan, H. J.; Liu, Q. *J. Org. Chem.* **2008**, *73*, 2442. (c) Bi, X. H.; Dong, D. W.; Liu, Q.; Pan, W.; Zhao, L.; Li, B. *J. Am. Chem. Soc.* **2005**, *127*, 4578. (d) Yadav, A. K.; Ila, H.; Junjappa, H. *Eur. J. Org. Chem.* **2010**, 338. (e) Yadav, A. K.; Peruncheralathan, S.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2007**, *72*, 1388.

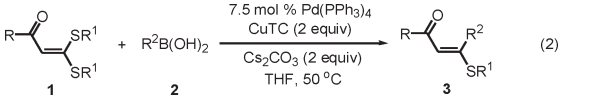
(15) (a) Yu, H. F.; Jin, W. W.; Sun, C. L.; Chen, J. P.; Du, W. M.; He, S. B.; Yu, Z. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 5792. (b) Yu, H. F.; Yu, Z. K. *Angew. Chem., Int. Ed.* **2009**, *48*, 2929.

(16) (a) Wang, Y. M.; Bi, X. H.; Li, W. Q.; Li, D. H.; Zhang, Q.; Liu, Q.; Ondon, B. S. *Org. Lett.* **2011**, *13*, 1722. (b) Yuan, H. J.; Wang, M.; Liu, Y. J.; Wang, L. L.; Liu, J.; Liu, Q. *Chem.—Eur. J.* **2010**, *16*, 13450. (c) Liang, D. Q.; Wang, M.; Bekturhun, B.; Xiong, B. B.; Liu, Q. *Adv. Synth. Catal.* **2010**, *352*, 1593. (d) Liu, Y. J.; Wang, M.; Yuan, H. J.; Liu, Q. *Adv. Synth. Catal.* **2010**, *352*, 884. (e) Yuan, H.-J.; Wang, M.; Liu, Y.-J.; Liu, Q. *Adv. Synth. Catal.* **2009**, *351*, 112.

(17) Zhang, S. J.; Zhang, D. W.; Liebeskind, L. S. *J. Org. Chem.* **1997**, *62*, 2312.

(18) Nishio, T.; Omote, Y. *J. Chem. Soc., Perkin Trans. 1* **1981**, 934.

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



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 ^1H NMR analysis in $CDCl_3$.

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 ^1H 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).

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

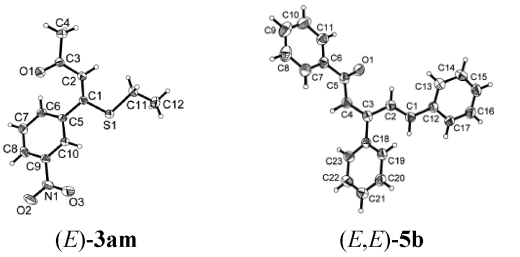
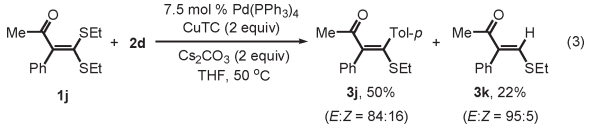
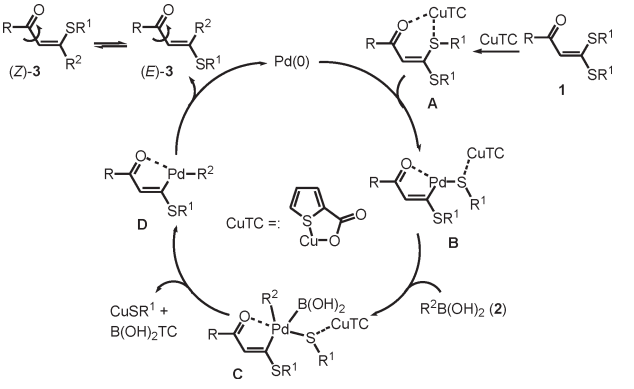


Figure 1. Crystal structures of (*E*)-**3am** and (*E*,*E*)-**5b**.



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**.

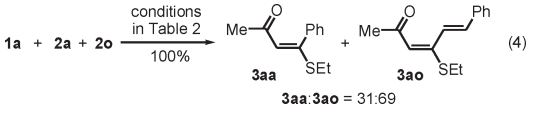
Scheme 1. A Proposed Mechanism



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

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]



(4)

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.

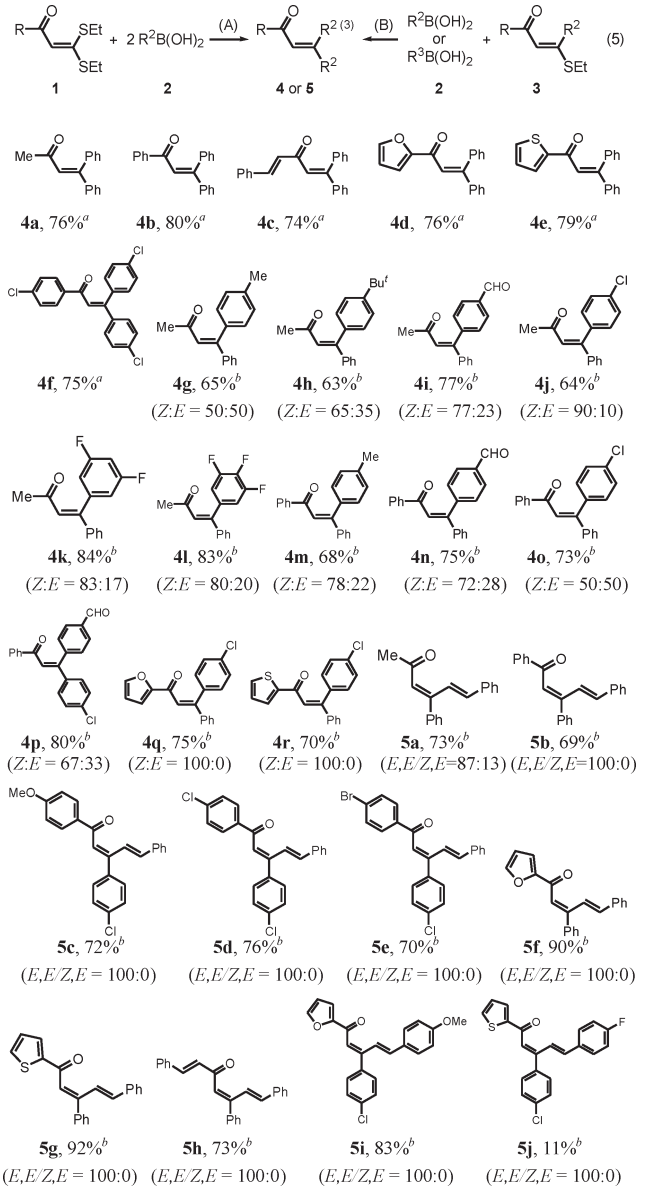


Figure 2. Cross-coupling of **1** or **3** with aryl and alkenylboronic acids **2**. Conditions: $Pd(PPh_3)_4$ (7.5 mol %), dppe (7.5 mol %), THF (5 mL), 50 °C, 13 h, 0.1 MPa N_2. Isolated yields and (*E*)/(*Z*) ratios determined by ^1H NMR analysis. [a]Conditions (A): **1** (0.5 mmol), **2** (2.0 mmol), 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.

(20) Gürtler, C.; Buchwald, S. L. *Chem.—Eur. J.* **1999**, *5*, 3107.