Organic LETTERS

Letter

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General Methodology for the Preparation of Unsymmetrical α-Linked Bisenones via Ligandless Cross-Coupling Reactions

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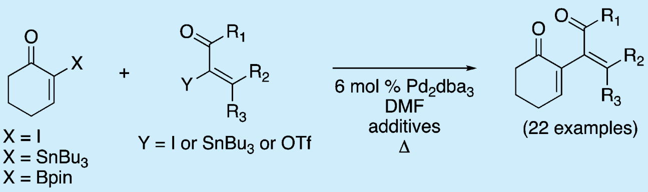
Supporting Information

ABSTRACT: A stereocontrolled Stille cross-coupling reaction, involving the use of Pd_2dba_3, provides a general procedure for the synthesis of unsymmetrical α-linked bisenone systems. The transformation is achieved in the absence of phosphine ligands under conditions that promote the stabilization of "ligandless" palladium catalysis. The extension of these studies illustrates Suzuki–Miyaura reactions of 2-boryl-2-cyclohexen-1-one with iodide and triflate partners for the synthesis of novel electron-deficient 1,3-dienes.



Cross-coupling reactions are widely utilized in synthesis applications owing to the broad scope and functional group compatibility of these processes.[1] While the development of catalysts and key parameters for general reactions of Csp^3 cross-coupling is a current topic of investigation,[2] cross-coupling reactions also provide opportunities for the generation of highly reactive molecular motifs.[3] Inspired by targeted studies of natural product synthesis, we recently explored general methodology for bonding of the α-carbon of an α,β-unsaturated carbonyl moiety **1** to the α-carbon of a second unsaturated Stille partner **2** to yield the cross-conjugated diene **3**. We generically refer to these products as "α-linked bisenones" (Figure 1). Our goal has sought to prepare unsymmetrical, electron-deficient 1,3-dienes as highly reactive components for applications in stereocontrolled annulations.

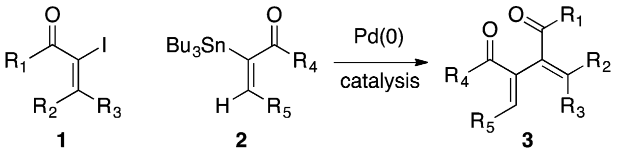
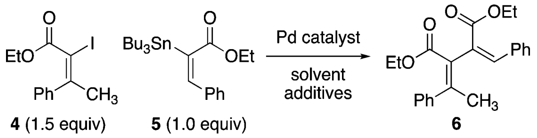


Figure 1. Formation of α-linked bisenones **3**.

Although specific examples of Stille cross-coupling reactions have been described to yield α-linked bisenones **3**,[4] our initial attempts to adapt these procedures failed entirely or led to low-yielding reactions in some instances. Because prior reports documented narrowly defined examples, we began a search for a general protocol to meet our needs. Herein, we communicate our studies of Stille cross-coupling reactions under "ligandless conditions", leading to a useful preparation of α-linked bisenones. These findings demonstrate the formation of a variety of electron-deficient, unsymmetrical dicarbonyl systems in reactions that occur with retention of olefin geometry. In addition, an extension of our studies includes specific examples of the Suzuki–Miyaura cross-coupling utilizing the analogous B-pin derivative to successfully obtain reactive α-linked bisenone products.

A condensed summary of initial studies of catalysts and conditions for the production of **3** is compiled in Table 1. The attempted Stille reaction of **4** and **5** was examined with the use of

Table 1. Summary of Optimization Studies[a]



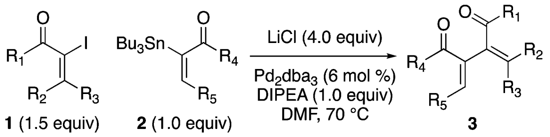
entry	catalyst (6 mol %)	additive (equiv)	ligand (equiv)	yield[b] (%)
1	$Pd(PPh_3)_4$	CuCl (5.0) LiCl (6.0)	none	0
2	$Pd(PPh_3)Cl_2$	CuI (0.8)	none	0
3	$Pd(PhCN)_2Cl_2$	CuI (0.8)	$AsPh_3$ (0.8)	29[c]
4	Pd_2dba_3	CuI (0.8)	$AsPh_3$ (0.8)	trace
5	Pd_2dba_3	CuI (0.1)	$AsPh_3$ (0.1)	trace
6	Pd_2dba_3	LiCl (4.0)	none	41
7	Pd_2dba_3	LiCl (4.0)	$AsPh_3$ (0.8)	5
8	Pd_2dba_3	LiCl (4.0)	tri(2-furyl)-phosphine (0.8)	0
9	Pd_2dba_3	LiCl (4.0) CuI (0.8)	none	38
10	Pd_2dba_3	LiCl (4.0)	TBAI (2.0)	55
11	Pd_2dba_3	LiCl (4.0)	DIPEA (1.0)	72

[a] Reactions were generally maintained at 70 °C for 6 h. Entry 1 was heated at 50 °C for 18 h, and entry 3 was stirred at 22 °C for 48 h. [b] Yields were determined by isolation of **6** followed by flash chromatography, and trace % was determined by ^1H NMR analysis of crude product mixture. [c] A 20% yield of the homodimer of **4** was also obtained.

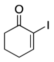
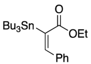
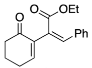
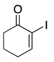
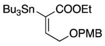
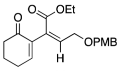
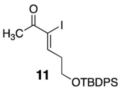
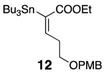
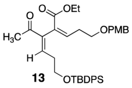
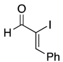
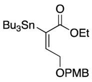
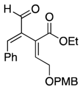
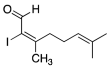
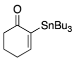
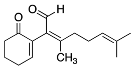
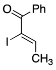
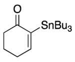
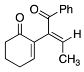
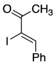
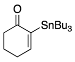
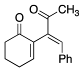
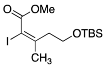
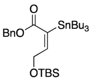
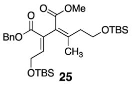
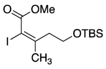
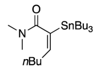
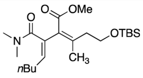
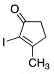
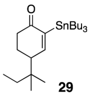
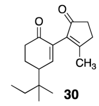
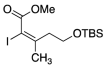
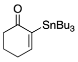
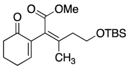
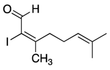
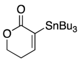
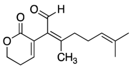
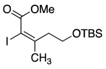
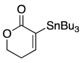
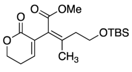
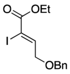
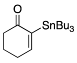
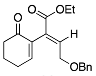
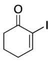
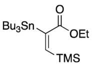
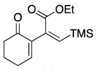
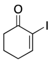
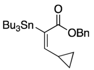
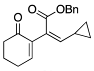
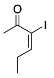
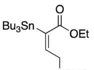
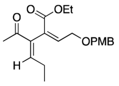
Received: February 17, 2017

DOI: 10.1021/acs.orglett.7b00497

Table 2. Stille Cross-Coupling To Yield Bisenones[a]



1 (1.5 equiv) **2** (1.0 equiv) **3**

entry	iodoenone	stannane	product	isolated yield %[b]
1	 **7**	 **5**	 **8**	63
2	 **7**	 **9**	 **10**	74
3	 **11**	 **12**	 **13**	76
4	 **14**	 **9**	 **15**	81
5	 **16**	 **17**	 **18**	63
6	 **19**	 **17**	 **20**	50
7	 **21**	 **17**	 **22**	80
8	 **23**	 **24**	 **25**	69
9	 **23**	 **26**	 **27**	71
10	 **28**	 **29**	 **30**	76
11	 **23**	 **17**	 **31**	65
12	 **16**	 **32**	 **33**	43
13	 **23**	 **32**	 **34**	61
14	 **35**	 **17**	 **36**	68
15	 **7**	 **37**	 **38**	52
16	 **7**	 **39**	 **40**	84
17	 **41**[c]	 **9**	 **42**	70

[a] The optimized reaction conditions of Table 1 were directly applied for each example by heating at 70 °C for 8 h. In some cases, reactions did not proceed to completion, and small quantities of stannane were recovered. [b] Yields are based on isolated product after flash silica gel chromatography. [c] Starting iodide **41** undergoes facile *E* → *Z* isomerization upon heating prior to cross-coupling.

$Pd(PPh_3)_4$ and $PhCH_2PdCl(PPh_3)_2$ catalysts in DMF or CH_3CN in the presence of CuI.[4a] In addition, the use of $Pd(PPh_3)_2Cl_2$ and CuI in DMF as described in the synthesis of xanthocillin X dimethyl ether by Tatsuta and Yamaguchi was explored.[4e] These attempts yielded several byproducts but none of the desired diene **6** (entries 1 and 2). Johnson et al.[5] have also reported the cross-coupling of α-iodoenones with alkenylstannanes and arylstannanes using bis(benzonitrile)palladium dichloride in NMP in the presence of $AsPh_3$ and CuI. The application of the latter conditions led to product mixtures containing substantial amounts of the homocoupled dimer of **4** (entry 3). A significant concern, with implications for our choice of a catalyst, is the production of polymeric materials via competing Heck processes leading to the destruction of the desired product and/or the starting enones. Our previous studies have reported the successful preparation of allenes by employing Pd_2dba_3 as an effective catalyst for Stille coupling of propargylic stannanes with α-iodocyclohexenone, as well as several heterocyclic iodides in the presence of $AsPh_3$ and CuI.[3b] The application of these conditions provided traces of desired **6**, whereas significant homocoupling of **4** was observed (entries 4 and 5, Table 1). In the absence of CuI and $AsPh_3$, modest yields (30−40%) of the diene **6** were obtained (entry 6).[6] Subsequent experiments reintroduced varying amounts of selected phosphines (examples include entries 7 and 8), and in all cases, the production of **6** was impeded. These efforts were increasingly focused on applications of "ligandless" palladium catalysis. In fact, colloidal palladium nanoparticles, stabilized in DMF, have been used to catalyze Stille cross-couplings with 0.1 mol % loading.[7] Adhesion and precipitation of palladium particles are avoided to stabilize the suspension of a reactive catalyst. To this end, we investigated several additives, including tetra-*n*-butylammonium iodide (TBAI), and found notable improvement with *N*,*N*-diisopropylethylamine (DIPEA; 1.0 equiv) in DMF at 70 °C under anhydrous conditions. The fast exchange between free and coordinated amine ligands with the surface of palladium particles has been shown by ^1H NMR studies as compared to coordinated phosphines. Reproducible yields of **6**

DOI: 10.1021/acs.orglett.7b00497

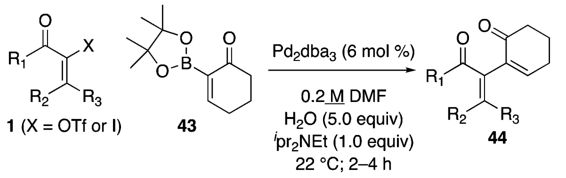
(Table 1, entry 11) have been obtained by the inclusion of anhydrous LiCl.

The scope of the reaction was examined using these conditions. A variety of unsymmetrical dicarbonyl derivatives were prepared including ketoaldehydes, bisenones, ketoesters, aldehydic esters, unsymmetrical esters, and amidoesters (Table 2). Highly substituted 1,3-dienes **3** were obtained using *Z*- or *E*-trisubstituted and tetrasubstituted α-iodoenones **1** and *Z*- or *E*-trisubstituted stannanes **2**. In this fashion, the preparation of stereodefined, tetrasubstituted olefins was accomplished with the formation of a highly functionalized product (entries 8−13, Table 2). The coupling reaction proceeded poorly using tetrasubstituted stannane components. Generally, the retention of stereochemistry was observed in our diene products, and we found no evidence for olefin isomerization as a result of the cross-coupling event. Whereas aliphatic α-iodoenones such as the (*E*)-3-iodo-3-hexen-2-one (**41**, entry 17) were prepared as single stereoisomers by *syn*-hydrostannation (3-hexyn-2-one) and replacement with iodine,[8] the less stable alkene **41** underwent facile thermal isomerization to the (*Z*)-olefin at 70 °C, which led to the cross-coupling product **42** (70%). The thermal isomerization of **41** proceeded slowly at 35 °C. At this temperature, the cross-coupling reaction required prolonged reaction times (>15 h) and thus produced *E*/*Z* mixtures of the diene product. In most experiments, a small amount of diene byproduct (5−15% yield) arose from homocoupling of the iodide partner **1**, and small quantities of protodestannylated enone (2−5%) were also observed. We note that Semmelhack and co-workers[9] previously described the homocoupling of methyl α-chloroacrylate with $Ni(COD)_2$ in ether. In addition, Liebeskind et al.[4a] also reported the palladium-catalyzed oxidative dimerization of 3-(tri-*n*-butylstannyl)-3-cyclobutene-1,2-diones to yield symmetrical bisquaryls.

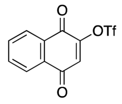
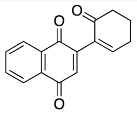
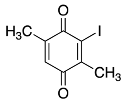
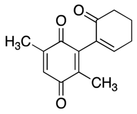
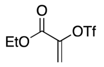
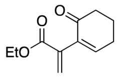
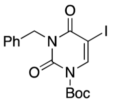
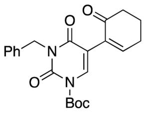
The α-iodo and α-stannyl unsaturated carbonyl components **1** and **2** were prepared using several methods. Iodides were routinely made by reacting the parent enone in CH_2Cl_2 and pyridine with I_2.[10] For sensitive substrates, this procedure was successfully modified by the addition of DMAP as the nucleophilic catalyst and K_2CO_3 to neutralize the protic acid generated during the reaction.[11] The α-iodo compounds **1** were also obtained in high yield by a cuprate addition to a starting alkynoate and quenching with I_2.[12] Additionally, the α-iodoenones **1** were generated by the reaction of a stabilized α-iodoylide with an aldehyde.[13] The stannanes **2** were prepared in good yield by halogen−metal exchange of the corresponding iodide with either a lithium or Grignard reagent followed by quenching with Bu_3SnCl.[12] Additionally, *syn*-reduction of an alkynoate using $n Bu_3SnH$ and $Pd(PPh_3)_4$ directly yielded the desired stannanes.[14] Alternatively, α-iodoenones **1** were transformed into stannanes **2** using a Stille coupling with bis(tributyltin) at elevated temperatures in the presence of catalytic $Pd(PPh_3)_4$.[15]

In the course of these studies, we encountered several attempts that failed to produce the expected diene products or led to a rapid decomposition of starting materials. To broaden the scope of our investigation, we revisited these examples using a Suzuki−Miyaura cross-coupling of the corresponding pinacol boronate (B-pin) **43** (Table 3). The substrates, illustrated in Table 3, provided product within 2−4 h at 22 °C in 0.2 M DMF solution in the presence of the Pd_2dba_3 catalyst and small amounts of water and *i*Pr_2NEt. The iodides **47** and **51** (entries 2 and 4) were prepared by known procedures,[16] and triflates **45** and **49** were obtained via O-acylation of the corresponding enols (entries 1 and 2). In general, the Suzuki−Miyaura applications are limited by the boronate availability. The 2-borylcyclohexenone **43** was prepared in four steps from cyclohexanone following the report of Cao and co-workers.[17] Recent studies of Lipshutz et al. have described the regiocontrolled hydroboration of acetylenic esters by a CuH-catalyzed *syn*-addition, which offers an advantageous pathway to (*Z*)-α-boryl α,β-unsaturated esters.[18] Overall, our studies suggest that unsymmetrical α-linked bisenones will be generally accessible via these prescribed Suzuki conditions.

Table 3. Selected Examples of Suzuki−Miyaura Reactions



1 (X = OTf or I) **43** **44**

entry	enone partner	product[a]	isolated yield %[b]
1	 **45**	 **46**	77
2	 **47**	 **48**	50
3	 **49**	 **50**	75
4	 **51**	 **52**	69

[a]The iodides (**47** and **51**) and triflates (**45** and **49**) were used in excess (4.0 equiv). Reactions at 22 °C showed complete consumption of the boronate **43** within 2−4 h. [b]Yields are determined for isolated product following flash chromatography and are based on starting **43**.

In summary, our studies have described a “ligandless” Stille cross-coupling process using Pd_2dba_3 for the preparation of unsymmetrical α-linked bisenone systems. Reactions broadly tolerate functionality, and retention of (*E*)- and (*Z*)-alkene geometry is generally observed. Additionally, the application of Suzuki−Miyaura reactions of 2-boryl-2-cyclohexenone with iodide and triflate derivatives have extended the methodology for synthesis of reactive α-linked bisenone systems. These highly unsaturated products provide novel opportunities for studies of new ring-forming reactions. Ongoing efforts will describe the use of these electron-deficient dienes for stereocontrolled annelation processes.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00497.

General information, experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This material is based upon work supported by the National Science Foundation under Grant No. CHE-1362561.

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