# A General Methodology for the Preparation of Unsymmetrical α-Linked Bis-enones via Ligandless Cross-Coupling Reactions

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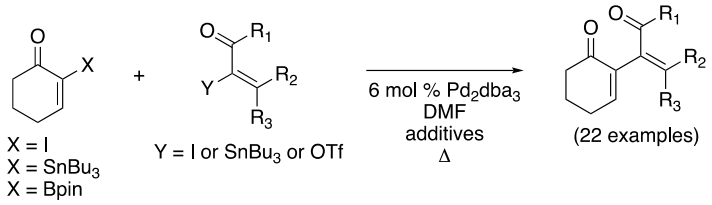
*Supporting Information Placeholder*




**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 bis-enone 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 are current topics 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 have 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 bis-enones" (Figure 1). Our goal has sought to prepare unsymmetrical, electron-deficient 1,3-dienes as highly reactive components for applications in stereocontrolled annulations.

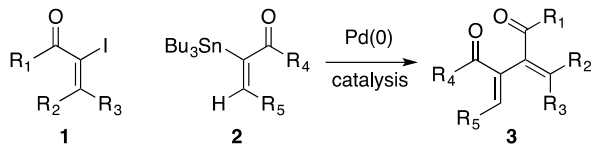


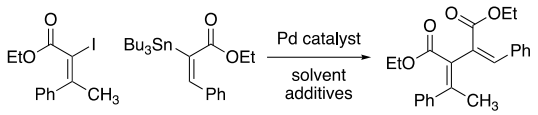

**Figure 1.** Formation of α-linked bis-enones **3**.

Although specific examples of Stille cross coupling reactions have been described to yield α-linked bis-enones **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 bis-enones. 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 bis-enone 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** has been examined with the use of $Pd(PPh_3)_4$ 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 has been 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 alkenyl stannanes 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 *a*-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** while 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

**Table 1. A Summary of Optimization Studies**[a]




**4** (1.5 equiv) **5** (1.0 equiv) **6**

| entry | catalyst (6 mol %) | additive (equiv) | ligand (equiv) | yield (%)[b] |
|---|---|---|---|---|
| 1 | $Pd(PPh_3)_4$ | CuCl (5.0)<br>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)<br>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 $^1$H NMR analysis of crude product mixture. [c]A 20% yield of homodimer of **4** was also obtained.

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 is 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 $^1$H NMR studies as compared to coordinated phosphines. Reproducible yields of **6** (Table 1; entry 11) have been obtained by the inclusion of anhydrous LiCl.

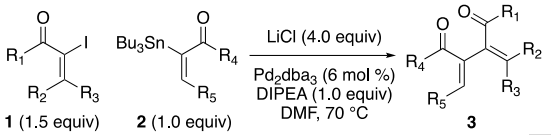
The scope of the reaction has been examined using these conditions. A variety of unsymmetrical dicarbonyl derivatives are prepared including ketoaldehydes, bis-enones, ketoesters, aldehydic esters, unsymmetrical esters, and amidoesters (Table 2). Highly substituted 1,3-dienes **3** are obtained using *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 is accomplished with the formation of a highly functionalized product (entries 8–13; Table 2). The coupling reaction proceeds poorly using tetrasubstituted stannane components. Generally, the retention of stereochemistry is observed in our diene products, and we find no evidence for olefin isomerization as a result of the cross-coupling event. While aliphatic α-iodo-enones such as the (*E*)-3-iodo-3-hexen-2-one (**41**, entry 17) are prepared as single stereoisomers by *syn*-hydrostannation (3-hexyn-2-one) and replacement with iodine,[8] the less stable alkene **41** undergoes facile thermal isomerization to the (*Z*)-olefin at 70 °C, which leads to the cross-coupling product **42** (70%). The thermal isomerization of **41** proceeds 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) arises from homocoupling of the iodide partner (**1**), and small quantities of protodestannylated enone (2–5%) may also be observed. We note that Semmelhack and coworkers[9] have previously described the homocoupling of methyl α-chloroacrylate with $Ni(COD)_2$ in ether. In addition, Liebeskind *et al.*[4a] have 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** have been 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** are also obtained in high yield by a cuprate addition to a starting alkynoate and quenching with $I_2$.[12] Additionally, the α-iodoenones **1** are generated by the reaction of a stabilized α-iodo ylide with an aldehyde.[13] The stannanes **2** are 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 yields the desired stannanes.[14] Alternatively, α-iodo enones **1** have been transformed into stannanes **2** using a Stille coupling with bis(tributyltin) at elevated temperatures in the presence of catalytic $Pd(PPh_3)_4$.[15]

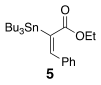
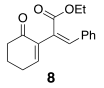
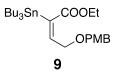
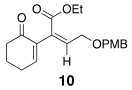
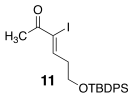
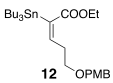
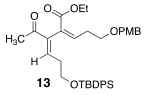
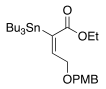
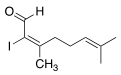
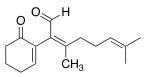
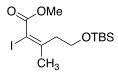
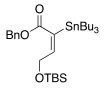
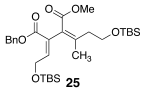
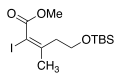
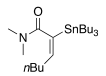
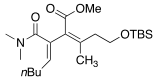
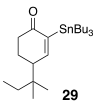
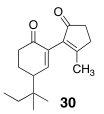
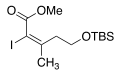
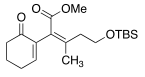
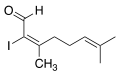
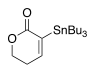
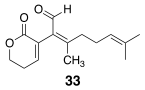
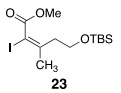
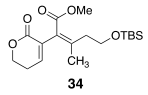
In the course of these studies, we encountered several attempts that failed to produce the expected diene products or led to a rapid decomposition of starting materials. To broaden the scope of our investigation, we have revisited these examples using a Suzuki–Miyaura cross coupling of the corresponding pinacol boronate (B-pin) **43** (Table 3). The substrates, illustrated in Table 3, provided product within 2 to 4 hours 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-boryl-cyclohexenone **43** was prepared in four steps from cyclohexanone following the report of Cao and coworkers.[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 bis-enones will be generally accessible via these prescribed Suzuki conditions.

**Table 2. Stille Cross-Coupling to Yield Bis-enones**[a]




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

| entry | iodenone | 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 with 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 $E \rightarrow Z$-isomerization upon heating prior to cross coupling.

**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 to 4 hours. [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 bis-enone 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 methodology for synthesis of reactive α-linked bis-enone 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.orglettxxxxxxx

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

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### Notes

The authors declare no competing financial interest.

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## REFERENCES

(1) For recent reviews: (a) Cordovilla, C.; Bartolomé, C.; Martínez-Ilarduya, J. M.; Espinet, P. *ACS Catal.* **2015**, *5*, 3040–3053. (b) Heravi, M. M.; Hashemi, E.; Azimian, F. *Tetrahedron* **2014**, *70*, 7–21. (c) Swift, E. C.; Jarvo, E. R. *Tetrahedron* **2013**, *69*, 5799–5817. (d) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4442–4489.

(2) (a) Dunsford, J. J.; Clark, E. R.; Ingleson, M. J. *Angew. Chem. Int. Ed.* **2015**, *54*, 5688–5692. (b) Steib, A. K.; Thaler, T.; Komeyama, K.; Mayer, P.; Knochel, P. *Angew. Chem. Int. Ed.* **2011**, *50*, 3303–3307. (c) Biswas, S.; Weix, D. J. *J. Am. Chem. Soc.***2013**, *135*, 16192–16197. (d) Guisán-Ceinos, M.; Soler-Yanes, R.; Collado-Sanz, D.; Phapale, V. B.; Buñuel, E.; Cárdenas, D. J. *Chem. Eur. J.* **2013**, *19*, 8405–8410. (e) Brand, G. J.; Studte, C.; Breit, B. *Org. Lett.* **2009**, *11*, 4668–4670. (f) Hossian, A.; Singha, S.; Jana, R. *Org. Lett.* **2014**, *16*, 3934–3937.

(3) For selected examples: (a) de Meijere, A.; Schelper, M.; Knoke, M.; Yucel, B.; Sünnemann, H. W.; Scheurich, R. P.; Arve, L. *J. Organomet. Chem.* **2003**, *687*, 249–255 (b) Williams, D. R.; Shah, A. A, *Chem. Commun.* **2010** *46*, 4297–4299. (c) Williams, D. R.; Morales-Ramos, Á. I.; Williams, C. M. *Org. Lett.* **2006** *8*, 4393–4396. (d) Nakamura, E. Isaka, M.; Matsuzawa, S. *J. Am. Chem. Soc.* **1988**, *110*, 1297–1298.

(4) (a) Liebeskind, L. S.; Yu, M. S.; Yu, R. H.; Wang, J.; Hagen, K. S. *J. Am. Chem. Soc.* **1993**, *115*, 9048–9055. (b) Zhang, G.; Peng, Y.; Cui, L.; Zhang, L. *Angew. Chem. Int. Ed.* **2009**, *48*, 3112–3115. (c) Patel, R. M.; Argade, N. P. *J. Org. Chem.* **2007** *72*, 4900–4904. (d) Wang, Q.; Yang, Y.; Li, Y.; Yu, W.; Hou, Z. J. *Tetrahedron* **2006**, *62*, 6107–6112. (e) Tatsuta, K.; Yamaguchi, T. *Tetrahedron Lett.* **2005**, *46*, 5017–5020. (f) Sai, H.; Ogiku, T.; Ohmizu, H.; Ohtani, A., *Chem. Pharm. Bull.* **2006**, *54*, 1686–1693. (g) Sai, H.; Ogiku, T.; Nishitani, T.; Hiramatsu, H.; Horikawa, H.; Iwasaki, T. *Synthesis* **1995**, 582–586. (h) Lee, J.-H.; Kim, W.-S.; Lee, Y. Y.; Cho, C.-G. *Tetrahedron Lett.* **2002**, *43*, 5779–5782.

(5) Johnson, C.; Adams, J.; Braun, M.; Senanayake, C. B. *Tetrahedron Lett.* **1991**, *33*, 919–922.

(6) After completion of this study, we were informed of two examples of related Stille coupling reactions using $Pd_2dba_3$ in DMF with $AsPh_3$ and copper iodide. See: (a) Chen, S.; Williams, R. M. *Tetrahedron* **2006**, *62*, 11572–11579. (b) Brooke, D. G.; Morris, J. C. *Tetrahedron Lett.* **2008**, *49*, 2414–2417.

(7) (a) Hyotanishi, M.; Isomura, Y.; Yamamoto, H.; Kawasaki, H.; Obora, Y. *Chem. Comm.* **2011**, *47*, 5750–5752. (b) Yano, H.; Nakajima, Y.; Obora, Y. *J. Organomet. Chem.* **2013**, *745–746*, 258–261.

(8) Zhang, H. X.; Guibé, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857–1867.

(9) (a) Semmelhack, M. F.; Helquist, P.; Jones, L. D.; Keller, L.; Mendelson, L.; Ryono, L. S.; Smith, J. G.; Stauffer, R. D. *J. Am. Chem. Soc.* **1981**, *103*, 6460–6471. (b) Kiji, J.; Okano, T.; Fujii, E.; Tsuji, *Synthesis* **1997**, 869–870.

(10) Bovonsombat, P.; Angara, G.; McNelis, E. *Tetrahedron Lett.* **1994**, *35*, 6787–6790.

(11) Krafft, M.; Cran, J. *Synlett* **2005**, 1263–1266.

(12) Orimoto, K.; Tomizawa, T.; Namera, Y.; Oyama, H.; Takashi, N.; Nakada, M. *Heterocycles* **2013**, *87*, 827–840.

(13) (a) Tanaka, K.; Kabayashi, T.; Mori, H.; Katsumura, S. *J. Org. Chem.* **2004**, *69*, 5906–5925. (b) Magnus, P.; Carter, R.; Davies, M.; Elliott, J.; Pitterna, T. *Tetrahedron* **1996**, *52*, 6283–6306.

(14) (a) Burke, B.; Overman, L. E. *J. Am. Chem. Soc.* **2004**, *126*, 16820–16833. (b) Bellina, F.; Carpita, A.; Ciucci, D.; De Santis, M.; Rossi, R. *Tetrahedron* **1993**, *49*, 4677–4698.

(15) Parker, K.; Wang, Z. *Org. Lett.* **2006**, *8*, 3553–3556.

(16) (a) Cressman, H. W. J.; Thirtle, J. R. *J. Org. Chem.* **1966**, *31*, 1279–1280. (b) Compound **51** was obtained by Boc protection of the commercially available iodide.

(17) Zhang, J.-T.; Qi, X.-L.; Chen, J.; Li, B-S.; Zhou, Y.-B.; Cao, X.-P. *J. Org. Chem.* **2011**, *76*, 3946–3959.

(18) (a) Lipshutz, B. H.; Boskovic, Z. V.; Aue, D. H. *Angew. Chem. Int. Ed.* **2008**, *47*, 10183–10186. (b) Semba, K.; Fujihara, T.; Terao, J.; Tsuji, Y. *Chem. Eur. J.* **2012**, *18*, 4179–4184.