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Synthesis of δ-Tributylstannyl-α,β,γ, δ-Unsaturated Aldehydes from Pyridines

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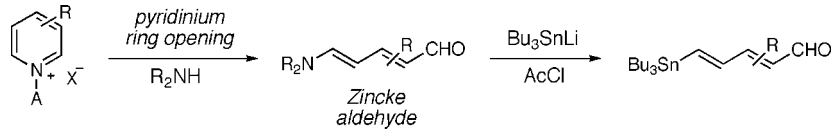
ABSTRACT



Zincke aldehydes, which are readily available from the ring-opening reaction of pyridinium salts, are easily converted into δ-tributylstannyl-α,β,γ,δ-unsaturated aldehydes (stannyldienals) by the action of tributylstannyllithium. This reaction appears to proceed via 1,6-stannyllithium addition/elimination of lithium dialkylamide. Several stannyldienals of significant utility for the synthesis of polyene natural products have been made by this route, which proceeds in modest yields, but is successful on multigram scale using inexpensive reagents. Simple stannylenals and stannylenones are similarly available from the corresponding vinylogous amides.

Polyene motifs are ubiquitous in biologically active and structurally novel natural products.[1] Cross-coupling reactions that forge sp^2-sp^2 bonds are particularly important for the efficient assembly of these important synthesis targets. In the arena of transition-metal-catalyzed cross-couplings, the Stille reaction has seen significant utility, largely as a result of the mild coupling conditions, and the relative stability and ease of handling of the requisite alkenylstannanes.[2]

γ-Tributylstannyl-α,β,γ,δ-unsaturated aldehydes (stannyldienals) and the corresponding esters have been used frequently in the synthesis of polyene natural products, including polyketides, retinoids, and carotenoids.[3,4] These reagents are typically made in several steps by radical stannylation or stannylcupration of alkynes, in conjunction with olefination and/or redox chemistry. Given the known compatibility of the aldehyde functional group with Stille cross-coupling conditions[2] and the stability of vinylstannanes to most aldehyde addition reactions, we posited that a short and general synthesis of bifunctional stannyldienals would

(1) Thirsk, C.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 999–1023.

(2) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1–652.

(3) Stannyldienals: (a) Yokokawa, F.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1993**, *34*, 6559–6562. (b) Andrus, M. B.; Lepore, S. D.; Turner, T. M. *J. Am. Chem. Soc.* **1997**, *119*, 12159–12169. (c) Domínguez, B.; Iglesias, B.; de Lera, A. R. *J. Org. Chem.* **1998**, *63*, 4135–4139. (d) Domínguez, B.; Iglesias, B.; de Lera, A. R. *Tetrahedron* **1999**, *55*, 15071–15098. (e) Pazos, Y.; Iglesias, B.; de Lera, A. R. *J. Org. Chem.* **2001**, *66*, 8483–8489. (f) Vaz, B.; Alvarez, R.; de Lera, A. R. *J. Org. Chem.* **2002**, *67*, 5040–5043. (g) Franci, X.; Martina, S. L. X.; McGrady, J. E.; Webb, M. R.; Donald, C.; Taylor, R. J. K. *Tetrahedron Lett.* **2003**, *44*, 7735–7740. (h) Burova, S. A.; McDonald, F. E. *J. Am. Chem. Soc.* **2004**, *126*, 2495–2500. (i) Sorg, A.; Brückner, R. *Synlett* **2005**, 289–293. (j) Vaz, B.; Alvarez, R.; Souto, J. A.; de Lera, A. R. *Synlett* **2005**, 294–298. (k) Webb, M. R.; Donald, C.; Taylor, R. J. K. *Tetrahedron Lett.* **2006**, *47*, 549–552. (l) Coleman, R. S.; Lu, X.; Modolo, I. *J. Am. Chem. Soc.* **2007**, *129*, 3826–3827. (m) Webb, M. R.; Addie, M. S.; Crawforth, C. M.; Dale, J. W.; Franci, X.; Pizzonero, M.; Donald, C.; Taylor, R. J. K. *Tetrahedron* **2008**, *64*, 4778–4791.

(4) Stannyldienoic esters: (a) Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434–9453. (b) Shinada, T.; Sekiya, N.; Bojkova, N.; Yoshihara, K. *Synlett* **1995**, 1247–1248. (c) Clark, A. J.; Ellard, J. M. *Tetrahedron Lett.* **1998**, *39*, 6033–6036. (d) Paquette, L. A.; Pissarnitski, D.; Barriault, L. *J. Org. Chem.* **1998**, *63*, 7389–7398. (e) Arimoto, H.; Nishimura, K.; Kuramoto, M.; Uemura, D. *Tetrahedron Lett.* **1998**, *39*, 9513–9516. (f) Wipf, P.; Coish, P. D. G. *J. Org. Chem.* **1999**, *64*, 5053–5061. (g) Pihko, P. M.; Koskinen, A. M. P. *Synlett* **1999**, 1966–1968. (h) Tanaka, K.; Katsumura, S. *Org. Lett.* **2000**, *2*, 373–375. (i) Olivo, H. F.; Velázquez, F.; Trevisan, H. C. *Org. Lett.* **2000**, *2*, 4055–4058. (j) Tanaka, K.; Mori, H.; Yamamoto, M.; Katsumura, S. *J. Org. Chem.* **2001**, *66*, 3099–3110. (k) Carson, M. W.; Kim, G.; Hentemann, M. F.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4450–4452. (l) Domínguez, B.; Vega, M. J.; Sussman, F.; de Lera, A. R. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2607–2609. (m) Esumi, T.; Okamoto, N.; Hatakeyama, S. *Chem. Commun.* **2002**, 3042–3043. (n) Hosoya, T.; Sumi, K.; Doi, H.; Wakao, M.; Suzuki, M. *Org. Biomol. Chem* **2006**, *4*, 410–415. See also refs 3b, d.

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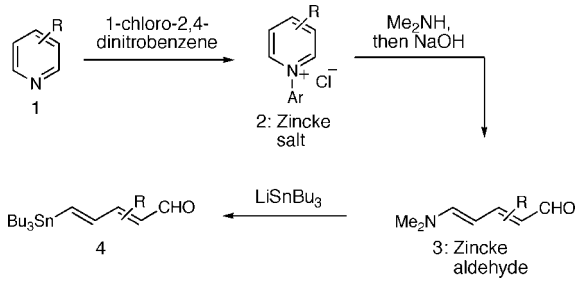
be of significant utility for the synthesis of polyene natural products. As part of our program to exploit the underappreciated, century-old Zincke procedure for the ring opening of pyridinium salts (**1** → **2** → **3**, Scheme 1),[5−7] we report a

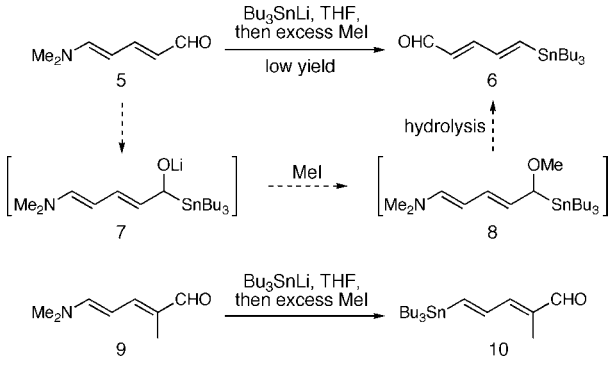
Scheme 1. Synthesis of Stannyldienals from Pyridines (Ar = 2,4-dinitrophenyl)



new method for the synthesis of stannyldienals (**4**) from pyridines. The key step is an unusual conjugate stannylation/amide anion elimination of 5-amino-2,4-pentadienals (Zincke aldehydes, **3**) derived from pyridinium salt ring-opening reactions. This general reaction also proceeds with other vinylogous amides to afford β-stannylenals and enones.

The known electrophilic nature of Zincke aldehydes[6a] prompted us to examine the regioselectivity of attack of tributylstannyllithium (Scheme 2).[8] Attempts to obtain vi-

Scheme 2. Regioselectivity of Stannylation of Zincke Aldehyde **9** Discounts 1,2-Addition/Hydrolysis Mechanism

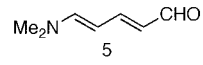
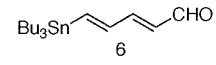
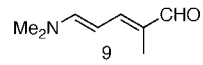
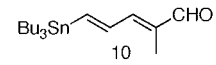
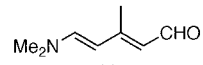
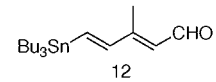
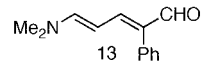
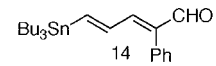
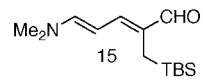
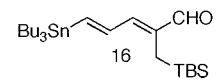


nylogous hemiaminal **8** by the sequential addition of tributylstannyllithium and methyl iodide led directly to the isolation of stannyldienal **6**[3d] in low yield; this result was initially attributed to a surprisingly facile hydrolysis of either **7** or **8** upon aqueous workup. However, the reaction of substituted Zincke aldehyde **9** under the same conditions furnished stannane **10**,[3m] consistent with a formal 1,6-addition/elimination reaction wherein dimethylamide anion had served as a leaving group. The tendency of stannylmetal nucleophiles to add in a conjugate fashion is well-known;[9] however, loss of dimethylamide anion as a leaving group is unusual.

If 1,6-addition/elimination is operative, then addition of methyl iodide should prove unnecessary; however, when aqueous acid was used in place of methyl iodide, no stannane product was observed. The addition of methyl iodide or another reactive electrophile is critical to the success of this reaction. Acetyl chloride emerged as the quenching agent of choice after a screen of acidic and electrophilic reagents; its low toxicity and cost also make it preferable to methyl iodide. The observation of dimethylacetamide in the crude reaction products suggests an important role for the electrophile in the removal of dimethylamide anion from the reaction mixture. In addition, the reaction appears to be reversible because exposure of pure stannyldienal **6** to lithium dimethylamide under otherwise identical reaction conditions led to the observation of small amounts of Zincke aldehyde **5** in the ^{1}H NMR spectrum of the crude reaction product.[10,11]

Table 1 shows several stannyldienals that have been synthesized from Zincke aldehydes according to the

Table 1. Stannyldienals From Zincke Aldehydes (TBS = *tert*-butyldimethylsilyl)

Zincke aldehyde	*stannane*	*yield*[a]
 5	 6	50–55%
 9	 10	60–67%
 11	 12	45–50%
 13 Ph	 14 Ph	35–38%
 15 TBS	 16 TBS	35–47%

[a] Range of isolated yields for reactions run on 0.5 to 2.0 mmol scales.

procedure optimized for substrate **9**. Methyl-substituted stannyldienals **10** and **12**[3d] are clearly relevant to the synthesis of polyketide and terpene-derived polyenes. The synthesis of phenyl-substituted stannyldienal **14** suggests that a range of aromatic substituents will be tolerated, and the

(5) (a) Zincke, T. *Liebigs Ann. Chem.* **1903**, *330*, 361–374. (b) Zincke, T. *Liebigs Ann. Chem.* **1904**, *333*, 296–345. (c) Zincke, T.; Wurker, W. *Liebigs Ann. Chem.* **1905**, *338*, 107–141. (d) König, W. *J. Prakt. Chem.* **1904**, *69*, 105–137.

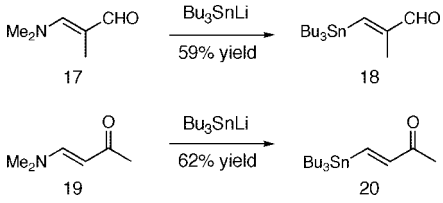
(6) For reviews of Zincke chemistry, see: (a) Becher, J. *Synthesis* **1980**, 589–611. (b) Cheng, W.-C.; Kurth, M. J. *Org. Prep. Proced. Int.* **2002**, *34*, 587–608. (c) Rojas, C. M. In *Name Reactions in Heterocyclic Chemistry*; Li, J. J., Ed.; John Wiley & Sons: Hoboken, NJ, 2005; pp 355−374.

(7) (a) Kearney, A. M.; Vanderwal, C. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 7803–7806. (b) Steinhardt, S. E.; Silverston, J. S.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2008**, *130*, 7560–7561.

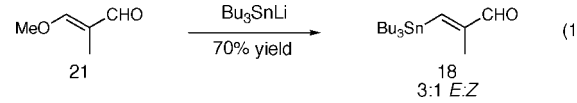
allylsilane of **16** might be harnessed for further C−C bond formation after reaction of the stannane and aldehyde functional groups. The modest and somewhat variable yields are offset by the simplicity of the chemistry that begins with cheap pyridines and uses tributyltin hydride as a relatively nontoxic and inexpensive tin source. We have run the stannylation reaction of **9** on 20 mmol scale in order to demonstrate preparative scale utility; stannane **10** was obtained in 58% yield (3.9 g), a result similar to that shown in Table 1.

Stannylenal **18**[12] and stannylenone **20**[13] were generated from the corresponding commercially available vinylogous amides **17** and **19** (Scheme 3). The formation of **20** demonstrates that the reaction is not limited to aldehydes; this result, along with the formation of **12**, demonstrates that the presence of relatively acidic protons in the substrate does not hamper this reaction. This is consistent with previous reports suggesting a low basicity for trialkylstannyl anion.[11,14]

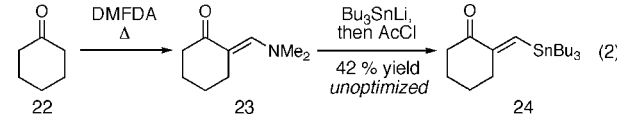
Scheme 3. Stannylation of Simple Vinylogous Amides



Commercially available vinylogous ester **21** also leads to the formation of stannane **18** in 70% yield (eq 1). In this case, an aqueous quench suffices, presumably as a result of the essentially irreversible nature of the reaction that generates an alkoxide leaving group, rather than an amide ion. The mixture of geometrical isomers obtained from **21**, compared with the stereochemically homogeneous product derived from vinylogous amide **17**, might be explained by the reversibility and potential for equilibration in the case of **17** (thermodynamic control) and the lack of equilibration with **21** (kinetic control).



One of many potential applications of the stannylation of vinylogous amides is a two-step α-stannylmethylenation of carbonyl compounds (eq 2). Readily accessible vinylogous amides such as **23**, which are derived in a high-yielding and general thermal reaction with dimethylformamide dimethyl acetal (DMFDA), serve as intermediates in this process.[15,16] Stannylmethylenation of **23** afforded **24**[17] in 42% unoptimized yield (≥10:1 *E:Z*).



Finally, since very few examples of the cross-coupling of trialkyltin-substituted unsaturated aldehydes have been reported,[18] and only one of a stannyldienal (**10**),[3j] we were compelled to demonstrate that this reaction could be readily achieved. Scheme 4 shows that coupling of stannane **12** with iodoalkene **25** under typical, unoptimized Stille conditions[19] affords **26** with the expected conservation of alkene geometries.[20] Additionally, stannane **14** and iodobenzene undergo Stille coupling under similar conditions to afford **27**.

Though the yields of our stannane syntheses are modest, the ready availability of the starting materials on large scale from pyridines or from commercial sources and the simplicity of the reaction conditions conspire to make this a very

(8) The regioselectivity of addition of trimethylstannyllithium to enones has been studied: Still, W. C.; Mitra, A. *Tetrahedron Lett.* **1978**, *19*, 2659–2662.

(9) The conjugate addition of tin anions and stannylcopper reagents, in particular, is well documented. For examples, some of which include conjugate addition/elimination reactions to generate vinylstannanes from acceptors that bear excellent *β*-leaving groups, see: (a) Piers, E.; Morton, H. E. *J. Chem. Soc., Chem. Commun.* **1978**, 1033–1034. (b) Piers, E.; Morton, H. E. *J. Org. Chem.* **1980**, *45*, 4263–4264. (c) Piers, E.; Chong, J. M.; Morton, H. E. *Tetrahedron Lett.* **1981**, *22*, 4905–4908. (d) Seitz, D. E.; Lee, S.-H. *Tetrahedron Lett.* **1981**, *22*, 4909–4912. (e) Imanieh, H.; MacLeod, D.; Quayle, P.; Zhao, Y.; Davies, G. M. *Tetrahedron Lett.* **1992**, *33*, 405–408.

(10) A related reaction was recently disclosed by Fleming and coworkers using $PhMe_2SiLi$ with simple vinylogous amides. In one particular case, these authors found that the inclusion of an activated alkyl halide was required for successful outcomes, but this observation was not attributed to the reversibility of the process, nor was a satisfying explanation found. See: Fleming, I.; Marangon, E.; Roni, C.; Russell, M. G.; Taliansky Chamudis, S. *Can. J. Chem.* **2004**, *82*, 325–332.

(11) For the reversibility of trialkylstannyl anion additions to unsaturated electrophiles, see: Cox, S. D.; Wudl, F. *Organometallics* **1983**, *2*, 184–185. See also ref 8.

(12) *E*-Vinylstannane **18** has only been made stereoselectively once, via a multistep sequence: Asano, M.; Inoue, M.; Watanabe, K.; Abe, H.; Katoh, T. *J. Org. Chem.* **2006**, *71*, 6942–6951.

(13) Stannane **20** is most frequently made by Lewis acid mediated acetylation of *trans*-1,2-bis(tributylstannyl)ethylene: (a) Peel, M. R.; Johnson, C. R. *Tetrahedron Lett.* **1986**, *27*, 5947–5950. It has been used in synthesis several times; for representative examples, see: (b) Johnson, C. R.; Kadow, J. F. *J. Org. Chem.* **1987**, *52*, 1493–1500. (c) Echavarren, A. M.; Pérez, M.; Castaño, A. M.; Cuerva, J. M. *J. Org. Chem.* **1994**, *59*, 4179–4185. (d) Winkler, J. D.; Holland, J. M.; Peters, D. A. *J. Org. Chem.* **1996**, *61*, 9074–9075.

(14) For discussions of the low pK_a of trialkylstannanes, see: (a) Gilman, H.; Marrs, O. L.; Trepka, W. J.; Diehl, J. W. *J. Org. Chem.* **1962**, *27*, 1260–1265. (b) Kuivila, H. G.; Lein, G. H., Jr *J. Org. Chem.* **1978**, *43*, 750–751.

(15) Vinylogous amides from ketones and amide acetals: Meerwein, H.; Florian, W.; Schon, G.; Stopp, G. *Liebigs Ann. Chem.* **1961**, *641*, 1–39.

(16) Tendency of ketone-derived vinylogous amides related to **23** to undergo conjugate addition/elimination with alkyllithium nucleophiles: Abdullah, R. F.; Fuhr, K. H. *J. Org. Chem.* **1978**, *43*, 4248–4250.

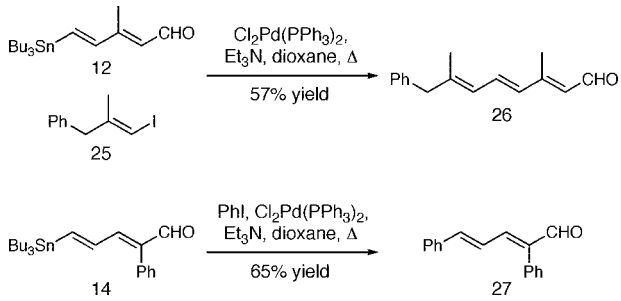
(17) Stannane **24** has been prepared by conjugate addition/elimination of the relevant *β*-iodoenone: Piers, E.; Morton, H. E.; Chong, J. M. *Can. J. Chem.* **1987**, *65*, 78–87.

(18) (a) Han, Q.; Wiemer, D. F. *J. Am. Chem. Soc.* **1992**, *114*, 7692–7697. (b) Bach, T.; Heuser, S. *Chem.—Eur. J.* **2002**, *8*, 5585–5592.

(19) The conditions in Scheme 4 were derived from those detailed in ref 18b.

(20) While stannyldienals with substituents α to the aldehyde such as **10** and **14** (and presumably **16**) generally cross-couple with retention of alkene geometries, stannane **12** readily isomerizes under Stille conditions, affording a mixture of product geometrical isomers. The inclusion of stoichiometric NEt_3 suppressed isomerization in the synthesis of **26**. A similar isomerization of the *Z*-isomer of **18** to the *E*-isomer under Stille conditions has been reported; see ref 18a.

Scheme 4. Representative, Unoptimized Stille Couplings of Stannanes **12** and **14**



attractive protocol for the generation of valuable building blocks for polyene synthesis. The use of relatively innocuous tributyltin hydride as a tin source (in place of the often used alternatives such as toxic tributyltin chloride or highly toxic and expensive hexamethylditin) is also advantageous. Finally, the products bear the desirable aldehyde functional group, which is fully compatible with Stille cross-coupling conditions and highly versatile in its own right. Without recourse to oxidation state adjustment, these stannyldienals can be readily converted into more complex stannanes.[3]

We disclose a simple and general synthesis of a variety of useful, bifunctional unsaturated molecules. The pivotal role played by the chemistry of the aldehyde functional group, along with the importance of the Stille reaction for polyene synthesis, renders these stannyldienals and related stannanes invaluable for polyene synthesis. It is also noteworthy that they are available in only three steps from pyridines, or in a single step from commercially available vinylogous amides, using common reagents. The availability of a range of substituted Zincke aldehydes from substituted pyridines renders facile access to complex stannyldienals that should prove versatile as linchpins for complex polyene synthesis, using the orthogonal chemistry of the stannane and the aldehyde.

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Supporting Information Available: Complete experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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