

# Stereoselective Synthesis of $\beta$ -(Chloro)vinylsilanes Using a Regio- and (*E*)-Stereoselective Bis-Stannylation of Unsymmetrically Substituted Butadiynes: Application to the Synthesis of a Masked Triyne

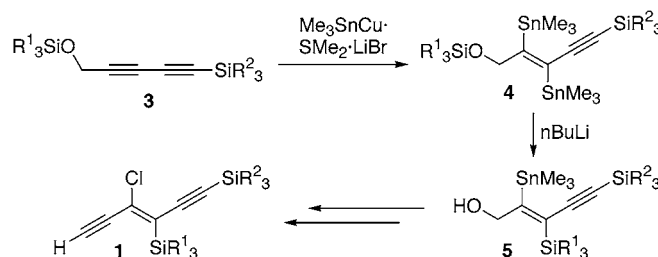
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## ABSTRACT



A highly regio- and stereoselective bis-stannylation of unsymmetrically substituted butadiyne **3** provides bis-stannane **4**. Selective lithiation of the internal tin residue effects a 1,4-retro-Brook rearrangement to afford vinylsilane **5**. This was elaborated into the novel diethynylethene **1**, which also functions as a masked triyne.

The shape and reactivity of the alkyne functional group, particularly when it is incorporated into highly conjugated systems and rings, can lead to problems in a synthesis. These can be circumvented by temporarily *masking* this functional group and releasing the alkyne at a later stage in the synthesis. A wide variety of approaches have been developed for achieving this type of masking strategy.<sup>1</sup>

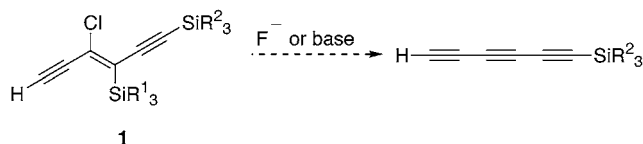
$\beta$ -(Halo)vinylsilanes are an attractive type of masked alkyne that have only rarely been used in synthesis.<sup>2</sup> Exposure to fluoride or base effects elimination and provides

a mild and selective route to the corresponding alkyne. We are interested in exploiting this type of protected alkyne functionality for synthesizing masked triynes for potential application in natural product synthesis, as well as for generating new monomeric building blocks for the preparation of nonaromatic, highly conjugated organic oligomers.<sup>3</sup> To this end, we required a synthesis of the masked triyne **1** (Scheme 1).

(1) (a) Tobe, Y.; Ohki, I.; Sonoda, M.; Niino, H.; Sato, T.; Wakabayashi, T. *J. Am. Chem. Soc.* **2003**, *125*, 5614–5615. (b) Eisler, S.; Chahal, N.; McDonald, R.; Tykwinski, R. R. *Chem. Eur. J.* **2003**, *9*, 2542–2550. (c) Adamson, G. A.; Rees, C. W. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1535–1543. (d) Diederich, F.; Rubin, Y. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1101–1123 and references therein. (e) Nicholas, K. M.; Pettit, R. *Tetrahedron Lett.* **1971**, 3475–3478.

(2) (a) Sueda, M.; Ichikawa, S.; Matsuda, A.; Shuto, S. *J. Org. Chem.* **2003**, *68*, 3465–3475. (b) Marshall, J. A.; Maxson, K. *J. Org. Chem.* **2000**, *65*, 630–633. (c) Schmitz, C.; Rouanet-Dreyfuss, A.-C.; Tueni, M.; Biellmann, J.-F. *J. Org. Chem.* **1996**, *61*, 1817–1821. (d) Shakespeare, W. C.; Johnson, R. P. *J. Am. Chem. Soc.* **1990**, *112*, 8578–8579. (e) Oda, H.; Sato, M.; Morizawa, Y.; Oshima, K.; Nozaki, H. *Tetrahedron* **1985**, *41*, 3257–3268. (f) Yamaguchi, R.; Kawasaki, H.; Yoshitome, T.; Kawanisi, M. *Chem. Lett.* **1982**, 1485–1486. (g) Danheiser, R. L.; Carini, D. J. *J. Org. Chem.* **1980**, *45*, 3925–3927. (h) Cunico, R. F.; Dexheimer, E. M. *J. Am. Chem. Soc.* **1972**, *94*, 2868–2869.

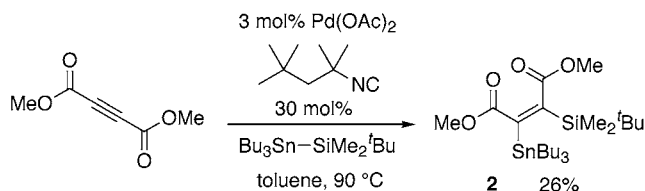
**Scheme 1.** (*E*)-4-Chloro-3-silylhex-3-ene-1,5-diyne as Masked Triynes



To maximize the flexibility of the end product, we set ourselves a number of conditions that our synthetic strategy would have to satisfy. We required the internal double bond to be a single (*E*)-stereoisomer, to facilitate dechlorosilylation, and that the termini of the appended alkynes be differentiated such that we could attach additional substituents to the framework in a sequential fashion.

After considering a number of approaches to **1**, it quickly became apparent that the lynchpin step would be that of incorporating the vinylsilane moiety. The direct installation of this functionality through a silylstannylation of an appropriately substituted alkyne was an attractive option which we examined first.<sup>4</sup> Palladium-catalyzed silylstannylation of alkynes is highly syn-selective,<sup>4</sup> although we hoped that isomerization to the desired thermodynamically more stable (*E*)-stereoisomer might be achievable in a number of ways at a later stage.<sup>4a,b</sup> Silylstannylation only works well on terminal alkynes or on internal alkynes that are activated with electron-withdrawing groups.<sup>4</sup> We therefore considered dimethyl acetylenedicarboxylate as a starting material that could potentially be elaborated into our target. Heating equimolar quantities of (*tert*-butyldimethylsilyl)tributylstannane<sup>4a</sup> and dimethyl acetylenedicarboxylate in the presence of Pd(OAc)<sub>2</sub> and 1,1,3,3-tetramethylbutyl isocyanide provided a single stereoisomeric product **2** in low yield<sup>5</sup> after prolonged (24 h) heating (Scheme 2).<sup>6</sup>

**Scheme 2.** Silylstannylation of Dimethyl Acetylenedicarboxylate



We were unable to improve upon this low yield and attributed the poor efficiency of the reaction to the steric

(3) (a) Poly(diacetylenes): Takayama, Y.; Delas, C.; Muraoka, K.; Sato, F. *Org. Lett.* **2003**, *5*, 365–368. (b) Poly(triacetylenes): Walker, J. A.; Bitler, S. P.; Wudl, F. *J. Org. Chem.* **1984**, *49*, 4733–4734. (c) Poly(pentaacetylenes): Schenning, A. P. H. J.; Arndt, J.-D.; Ito, M.; Stoddart, A.; Schreiber, M.; Siemsen, P.; Martin, R. E.; Boudon, C.; Gisselbrecht, J.-P.; Gross, M.; Gramlich, V.; Diederich, F. *Helv. Chim. Acta* **2001**, *84*, 296–334.

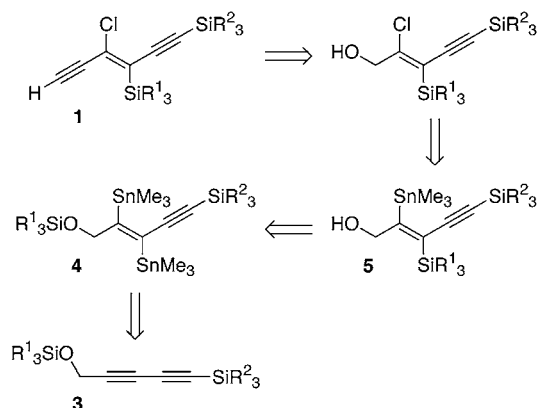
(4) (a) Chenard, B. L.; van Zyl, C. M. *J. Org. Chem.* **1986**, *51*, 3561–3566. (b) Mitchell, T. N.; Wickenkamp, R.; Amamria, A.; Dicke, R.; Schneider, U. *J. Org. Chem.* **1987**, *52*, 4868–4874. (c) For a review: Sugimoto, M.; Ito, Y. *Chem. Rev.* **2000**, *100*, 3221–3256.

bulk of the silyl substituents hindering reaction of the internal alkyne with the Si–Pd–Sn intermediate.<sup>4,6</sup> This did not bode well for future studies where we require the incorporation of silyl groups containing even bulkier substituents. We therefore sought an alternative approach.

Bis-stannylation of alkynes is one of the most widely used metal-metalation reactions.<sup>7</sup> Like silylstannylation, it is usually a palladium-catalyzed syn-selective process and also proceeds best on terminal alkynes or activated internal alkynes.<sup>7</sup> We were attracted to an intriguing alternative methodology employing copper mediation. Zweifel and Leong have reported that unsymmetrically substituted butadiynes react with the stannylcopper species, Me<sub>3</sub>SnCu·SMe<sub>2</sub>·LiBr, in a highly regio- and stereoselective fashion to afford (*E*)-bis-stannane products directly.<sup>8</sup> Furthermore they went on to show that the internal stannyl substituent could be selectively lithiated and trapped with simple electrophiles.<sup>8</sup> We envisaged that we might be able to apply this methodology, which had previously been demonstrated on only two simple examples, to a system that would allow subsequent elaboration into our target molecule **1**.

Our retrosynthesis is outlined in Scheme 3. Bis-stannylation of the unsymmetrically substituted butadiyne **3** would

**Scheme 3.** Retrosynthetic Analysis for Masked Triyne **1** Employing an (*E*)-Selective Bis-stannylation



provide bis-stannane **4**. Selective monolithiation at the internal site would then generate a nucleophilic vinyl lithium species set up to undergo a 1,4-retro-Brook rearrangement,<sup>9</sup> installing the vinyl silane **5** in a regioselective fashion and

(5) We have assigned the (*Z*)-configuration of the olefin in **2** on the basis of literature precedence (ref 4). A reviewer has suggested that the low yield of **2** may be due to the formation of byproducts from the reaction between the acetylenedicarboxylate and the isocyanide ligand.

(6) Murakami, M.; Amii, H.; Takizawa, N.; Ito, Y. *Organometallics* **1993**, *12*, 4223–4227.

(7) Beletskaya, I.; Moberg, C. *Chem. Rev.* **1999**, *99*, 3435–3461.

(8) Zweifel, G.; Leong, W. *J. Am. Chem. Soc.* **1987**, *109*, 6409–6412.

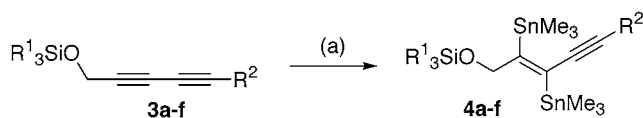
(9) (a) Baudoux, G.; Norberg, B.; Bousbaa, J.; Krief, A.; Evrard, G. *Acta Crystallogr. Sect. C* **1998**, *54*, 1944–1945. (b) Gibson, C.; Buck, T.; Walker, M.; Brückner, R. *Synlett* **1998**, 201–205. (c) Behrens, K.; Kneisel, B. O.; Noltemeyer, M.; Brückner, R. *Liebigs Ann.* **1995**, 385–400. (d) Lautens, M.; Delanghe, P. H. M.; Goh, J. B.; Zhang, C. H. *J. Org. Chem.* **1992**, *57*, 3270–3272. (e) Kim, K. D.; Magriotis, P. A. *Tetrahedron Lett.* **1990**, *31*, 6137–6140. (f) Rücker, C. *Tetrahedron Lett.* **1984**, *25*, 4349–4352.

at the same time freeing up the alcohol for subsequent elaboration into the second alkyne.

We considered this approach to be attractive for a number of reasons. In particular, we hoped that tethering the latent silyl electrophile to the proximal alcohol, thereby allowing installation of the vinylsilane through an intramolecular delivery pathway,<sup>10</sup> might prove especially beneficial for incorporating less electrophilic silyl groups containing bulkier substituents, which we require for a later stage of our research program. Furthermore, since the two alkyne substituents would be incorporated in separate stages we would satisfy the second of our design criteria, namely that we could differentiate the two alkyne termini.

At the outset, we did not know how the propargylic silyloxy group might affect the regio- and stereoselectivity of the bis-stannylation reaction. We were therefore delighted to observe that reaction of the stannylcopper reagent, prepared from equimolar quantities of Me<sub>3</sub>SnLi and CuBr·Me<sub>2</sub>S,<sup>11</sup> with butadiyne **3a**<sup>12</sup> at -50 °C, provided the desired bis-stannane **4a** as a single stereo- and regioisomer in very good yield. We used <sup>119</sup>Sn NMR to confirm the stereochemistry of this product. A <sup>3</sup>J<sub>119Sn-119Sn</sub> coupling constant of 686 Hz falls within the range expected for a trans-substituted bis-vinylstannane (coupling constants for cis-substituted bis-stannanes are generally lower than 500 Hz).<sup>13</sup> The selectivity was equally good for both TMS- and TIPS-substituted butadiynes and was not affected by the size of the silyl ether substituent with TES, TIPS, and TBDPS ethers all providing the desired bis-stannylated product **4** (Scheme 4).

**Scheme 4.** Stereo- and Regioselective Bis-stannylation of Aryl- and Silyl-Substituted Butadiynes<sup>a</sup>



- |          |   |          |  |
|----------|---|----------|--|
| <b>a</b> | R <sup>1</sup> <sub>3</sub> = Et <sub>3</sub> , R <sup>2</sup> = Si <sup>i</sup> Pr <sub>3</sub>  | <b>e</b> | R <sup>1</sup> <sub>3</sub> = <sup>t</sup> BuPh <sub>2</sub> , R <sup>2</sup> = Ph |
| <b>b</b> | R <sup>1</sup> <sub>3</sub> = Et <sub>3</sub> , R <sup>2</sup> = SiMe <sub>3</sub>                | <b>f</b> | R <sup>1</sup> <sub>3</sub> = Et <sub>3</sub> ,                                    |
| <b>c</b> | R <sup>1</sup> <sub>3</sub> = <sup>i</sup> Pr <sub>3</sub> , R <sup>2</sup> = SiMe <sub>3</sub>   |          | R <sup>2</sup> = 3,5-(BnOCH <sub>2</sub> ) <sub>2</sub> Ph                         |
| <b>d</b> | R <sup>1</sup> <sub>3</sub> = <sup>t</sup> BuPh <sub>2</sub> , R <sup>2</sup> = SiMe <sub>3</sub> |          |  |

<sup>a</sup> Reaction conditions: (a) Me<sub>3</sub>SnCu·SMe<sub>2</sub>·LiBr (2.6 equiv), THF, -50 °C **4a** (89%), **4b** (54%), **4c** (48%), **4d** (82%), **4e** (75%), **4f** (64%).

It is tempting to propose that the presence of the silicon protecting group at the diyne terminus governs the regio-

(10) For a review on the use of a temporary connection in synthesis: Cox, L. R.; Ley, S. V. In *Templated Organic Synthesis*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1999; Chapter 10, pp 275–395.

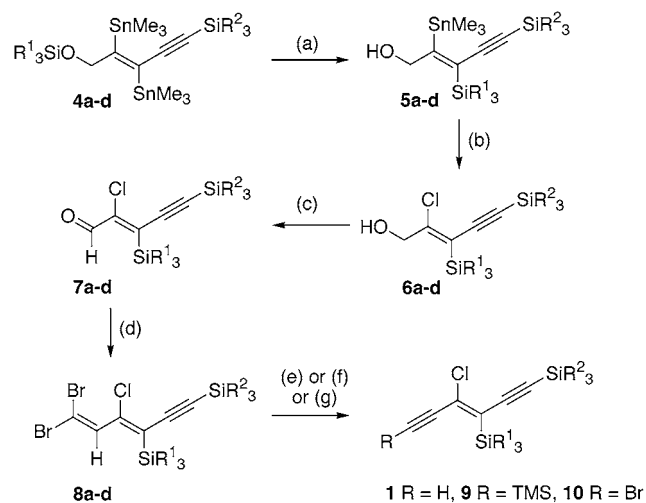
(11) San Filippo, J., Jr.; Silbermann, J. *J. Am. Chem. Soc.* **1982**, *104*, 2831–2836.

(12) Silyl ethers **3** were prepared from the corresponding alcohols. **3a**: Marino, J. P.; Nguyen, H. N. *J. Org. Chem.* **2002**, *67*, 6841–6844. **3b–d**: Holmes, A. B.; Jennings-White, C. L. D.; Schulthess, A. H.; Akindé, B.; Walton, D. R. M. *J. Chem. Soc., Chem. Commun.* **1979**, 840–842.

selectivity of the key bis-stannylation by sterically blocking the proximal alkyne group.<sup>14</sup> To investigate this further we prepared butadiynes **3e** and **3f** in which aryl substituents replaced the silyl groups as terminating species. Bis-stannylation of both diynes under the standard reaction conditions provided bis-stannanes **4e** and **4f** with the same regio- and stereochemical outcome as before (Scheme 4). The factors affecting the regioselectivity of this bis-stannylation and its extension to related systems will be the focus of future studies.

We were aware that the presence of an electron-withdrawing silyloxy substituent and its potential directing ability could also affect the regioselectivity of the subsequent lithiation step. However, treatment of **4** with 1.0 equiv of <sup>n</sup>BuLi provided the desired 1,4-retro-Brook rearrangement product **5** in good yield (Scheme 5).<sup>9</sup> Use of MeLi (low

**Scheme 5.** Synthesis of Masked Triynes **1**<sup>a</sup>



- a**, R<sup>1</sup><sub>3</sub> = Et<sub>3</sub>, R<sup>2</sup> = <sup>i</sup>Pr; **b**, R<sup>1</sup><sub>3</sub> = Et<sub>3</sub>, R<sup>2</sup> = Me;  
**c**, R<sup>1</sup><sub>3</sub> = <sup>i</sup>Pr<sub>3</sub>, R<sup>2</sup> = Me; **d**, R<sup>1</sup><sub>3</sub> = <sup>t</sup>BuPh<sub>2</sub>, R<sup>2</sup> = Me

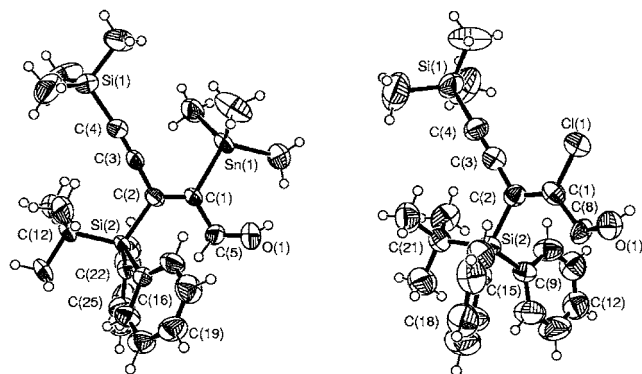
<sup>a</sup> Reaction conditions: (a) <sup>n</sup>BuLi (1.0 equiv), THF, -78 °C, **5a** (60%), **5b** (50%), **5c** (58%), **5d** (68%); (b) CuCl<sub>2</sub> (2.2 equiv), THF, 0 °C to rt, **6a** (74%), **6b** (98%), **6c** (97%), **6d** (99%); (c) MnO<sub>2</sub> (20 equiv), CH<sub>2</sub>Cl<sub>2</sub>, rt, **7a** (84%), **7b** (95%), **7c** (99%), **7d** (89%); (d) CBr<sub>4</sub> (2.0 equiv), PPh<sub>3</sub> (4.0 equiv), CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, **8a** (89%), **8b** (89%), **8c** (99%), **8d** (76%); (e) LDA (6.0 equiv), THF, -78 °C, **1a** (84%), **1b** (97%), **1c** (97%), **1d** (98%); (f) LDA (6.0 equiv), TMSCl (10.0 equiv), THF, -78 °C, **9b** (79%), **9c** (93%), **9d** (95%); (g) NaHMDS (1.1 equiv), THF, -78 °C, **10d** (70%).

chloride concentration) led to no significant improvement in yield, while an excess of <sup>n</sup>BuLi led to appreciable quantities of the bis-protodestannylated product. A crystal structure of **5d** confirmed the regioselectivity of the lithiation

(13) (a) Betzer, J.-F.; Le Ménez, P.; Prunet, J.; Brion, J.-D.; Ardisson, J.; Pancrazi, A. *Synlett* **2002**, 1–15. (b) Mitchell, T. N.; Nettelbeck, C. *Magn. Reson. Chem.* **1987**, *25*, 879–882. (c) Mitchell, T. N.; Amamria, A. *J. Organomet. Chem.* **1983**, *252*, 47–56.

(14) Hwu, J. R.; Wang, N. *Chem. Rev.* **1989**, *89*, 1599–1615. We acknowledge that electronic effects may also be important in controlling the regioselectivity of this reaction.

and that silylation had proceeded with retention of configuration (Figure 1). Subsequent elaboration of **5** into our target



**Figure 1.** ORTEP plots of **5d** (left) and **6d** (right) confirming the stereochemistry of the internal olefin. Atomic displacement parameters at 293 K.

molecule was straightforward (Scheme 5). Chlorodestannylation of the remaining tin residue with  $\text{CuCl}_2$  installed the vinyl chloride **6**.<sup>15</sup> A crystal structure of **6d** again confirmed that this reaction had also proceeded as expected in a stereospecific fashion with retention of configuration (Figure 1).

Allylic oxidation to the aldehyde **7** with  $\text{MnO}_2$  and subsequent dibromoolefination<sup>16</sup> both proceeded uneventfully to provide dibromoolefin **8** in excellent yield (Scheme 5). This underwent a Fritsch–Buttenberg–Wiechell rearrangement<sup>17</sup> on exposure to an excess of LDA at  $-78^\circ\text{C}$  to provide the target acetylene **1** in excellent yield, as evidenced by the appearance of a characteristic acetylenic C–H stretch

(15) (a) Madec, D.; F  r  zou, J.-P. *Tetrahedron Lett.* **1997**, *38*, 6661–6664. (b) Takeda, T.; Kanamori, F.; Matsusita, H.; Fujiwara, T. *Tetrahedron Lett.* **1991**, *32*, 6563–6566.

(16) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769–3772.

at  $3308\text{ cm}^{-1}$  in the IR spectrum of **1b**. The lithiated acetylene intermediate in this rearrangement could also be trapped with TMSCl to provide a more stable silylalkyne **9** in excellent yield. Furthermore, by replacing the LDA base with NaHMDS we were able to isolate the  $\text{E}_2$ -elimination product **10**.<sup>18</sup> This bromoalkyne further increases the number of cross-coupling strategies available for subsequent elaboration of this system.<sup>19</sup>

In summary, we have described a general synthesis of a novel diethynylethene containing an internal trans-substituted  $\beta$ -(chloro)vinylnsilane. The key step involves a highly regio- and (*E*)-stereoselective bis-stannylation of an unsymmetrically substituted butadiyne. This transformation allows the sequential installation of the silyl and chloro groups in a selective and predictable fashion through a relatively unusual 1,4-retro-Brook rearrangement and a stereospecific chlorodestannylation reaction using  $\text{CuCl}_2$ , respectively. Since the two pendant alkynes have been incorporated in a sequential fashion, this also ensures that the termini of our target diethynylethene are differentiated, which allows us to elaborate our products in a unidirectional fashion. We are currently investigating methods for incorporating this masked alkyne into long-chain conjugated organic molecules.

**Acknowledgment.** We are grateful to the Leverhulme Trust (F/00 094/T) for financial support and a postdoctoral research fellowship to S.M.E.S. and to the University of Birmingham for a studentship to C.A.

**Supporting Information Available:** General experimental procedures for **4–8**, **1**, **9**, and **10**, representative spectra for **1d**, **4d–10d**, and **4a,e**, and X-ray crystallographic files (in CIF format) for compounds **5d** and **6d**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(17) (a) Fritsch, P. *Liebigs Ann. Chem.* **1894**, *272*, 319–323. (b) Buttenberg, W. P. *Liebigs Ann. Chem.* **1894**, *272*, 324–337. (c) Wiechell, H. *Liebigs Ann. Chem.* **1894**, *272*, 337–344. (d) K  brich, G. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 49–68.

(18) Boden, C. D. J.; Pattenden, G.; Ye T. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2417–2419.

(19) *Metal-catalysed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998.