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A Novel "Double-Coupling" Strategy for Iterative Oligothiophene Synthesis Using Orthogonal Si/Ge Protection

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ABSTRACT

A new iterative synthesis of regioregular oligothiophenes has been developed in which "double-coupling" after each iteration minimizes deletion sequences. The method exploits the susceptibility of α-silyl- but not α-germyl-substituted thiophene derivatives toward nucleophilic *ipso*-protodemetalation and features an unusual "base-free" Suzuki-type cross-coupling protocol. The strategy has been designed for the *solid-phase* synthesis of high purity oligothiophenes using a germanium-based linker.

π-Conjugated heterocylic oligomers such as regioregular oligo-(β-alkylthiophenes), related block co-oligomers, and polymers display electronic properties that make them promising constituents of organic field effect transistors.[1] Such devices hold great potential for the development of simple, low cost, "disposable electronics" items such as electronic price tags. Suitability for such applications depends critically on these materials' displaying reproducibly high carrier mobilities ($>10^{-2}$ cm^2/Vs) and being amenable to simple, large area, solution processing technologies (e.g., ink-jet printing).[2] Backbone defects, deletion sequences, and trace impurities are highly detrimental to achieving high carrier mobilities, and these imperfections must be minimized during synthesis and through purification.

Traditional approaches toward regioregular oligo-(β-alkylthiophenes) of well-defined length rely on repetitive transition metal catalyzed cross-coupling of thiophene monomers in solution with careful purification of chromatographically similar intermediates following each successive iteration, a process which is time-consuming and inefficient.[3]

Recent publications applying solid-phase synthesis (SPS) to the iterative preparation of oligothiophenes demonstrate that SPS offers an attractive solution to some of the purification issues.[4] However, the ultimate purity of the cleaved oligomer is critically dependent on the yields attained for each individual cross-coupling step. Incomplete cross-coupling results in deletions and leads to a distribution in the final oligomer length.

In this communication we describe our development of a novel strategy by which optimum cross-coupling efficiencies can be ensured for each iteration (i.e., addition of each successive thiophene monomer) through double-coupling. By double-coupling, we mean reactivation and recoupling following an initial coupling to drive each iteration to completion.[5] This is only possible if the α-position of the newly

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(1) Reviews: (a) Katz, H. E.; Bao Z.; Gilat, S. L. *Acc. Chem. Res*. **2001**, *34*, 359−369. (b) Dimitrakopoulos, C. D.; Mascaro, D. J. *IBM J. Res. Dev*. **2001**, *45*, 11−27.

(2) (a) Bao, Z.; Dodabalpur, A.; Lovinger, A. *Appl. Phys. Lett*. **1996**, *69*, 4108−4110. (b) Bao, Z.; Lovinger, A. J. *Chem. Mater*. **1999**, *11*, 2607−2612. (c) Sirringhaus, H.; Tessler, N.; Friend, R. H. *Science* **1998**, *280*, 1741−1744.

(3) Bäuerle, P. In *Handbook of Oligo-Polythiophenes*; Fichou, D., Ed.; Wiley-VCH: Weinheim, **1999**; 89−181.

(4) (a) Malenfrant, P. R. L.; Fréchet, J. M. J. *Chem. Commun*. **1998**, 2657−2658. (b) Huang, H.; Tour, J. M. *J. Org. Chem*. **1999**, *64*, 8898−8906. (c) Briehn, C. A.; Kirschbaum, T.; Bäuerle, P. *J. Org. Chem*. **2000**, *65*, 352−359. (d) Kirschbaum, T.; Briehn, C. A.; Bäuerle, P. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1211−1216. (e) Kirschbaum, T.; Bäuerle, P. *Synth. Met*. **2001**, *119*, 127−128. (f) Briehn, C. A.; Schiedel, M.-S.; Bonsen, E. M.; Schuhmann, W.; Bäuerle, P. *Angew. Chem., Int. Ed*. **2001**, *40*, 4680−4683.

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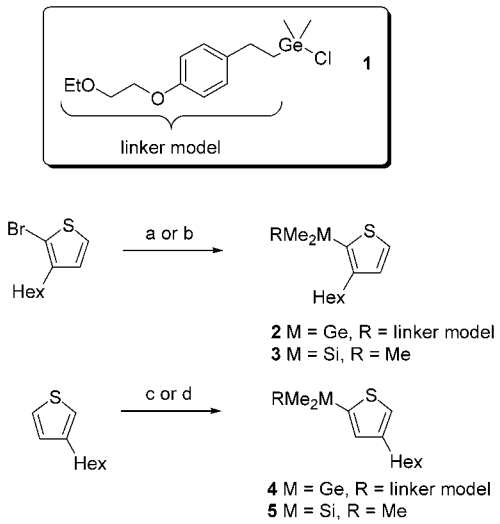
introduced monomer that becomes the terminus of the growing oligomer is protected toward activation by a temporary "blocking" group. To achieve this, we employ a germanium-based linker[6] to attach the growing oligothiophene to the solid support and use a trimethylsilyl (TMS) temporary blocking group to protect the α-position of the introduced thiophene unit. The success of the strategy is crucially dependent on the fact that the temporary TMS blocking group can be deprotected (i.e., removed) without affecting the linkage to the solid support. As such, the method relies on the orthogonal susceptibility of α-silyl- and α-germyl-substituted thiophene-derivatives toward nucleophilic *ipso*-protodemetalation (vide infra).[7] The germanium-based linker also allows for final cleavage by electrophilic *ipso*-degermylation.[5] Cleavage with acid will yield α-H terminated oligomers, whereas cleavage with halonium ions will yield α-halo terminated oligomers.[5] Such α,ω-differentiated telechelic oligomers are valuable substrates for block co-oligomer preparation and for oligomer end-capping.[8]

Readily available chlorogermane **1**,[9] which we have used previously as a solution-phase model linker system to develop methodology for SPS, was reacted with 4- and 3-hexyl-2-lithiothiophenes to give germylthiophenes **2** and **4**, respectively. Analogous TMS thiophenes **3** and **5** were similarly prepared from TMSCl (Scheme 1).

Scheme 1[a]



[a] (a) *n*-BuLi, THF, −78 °C; **1** (72%). (b) *n*-BuLi, THF, −78 °C; Me_3SiCl (87%). (c) LDA, THF, −50 °C; **1** (60%). (d) LDA, THF, −50 °C; Me_3SiCl (98%).

Our first objective was to establish conditions under which an immobilized α-silylthiophene could be deprotected (*ipso*-protodesilylated) without affecting the α-germyl linkage. As arylgermanes are known to be substantially more stable toward nucleophiles than their arylsilane counterparts,[10] we screened a number of nucleophilic conditions to achieve this goal. Screening comprised ^{1}H NMR monitoring of *ipso*-protodemetalation of α-germylthiophenes **2** and **4** vs α-TMS-thiophenes **3** and **5** while the temperature was stepped up from 25 to 60 to 110 °C over 72 h. Both K_3PO_4 and CsF in DMF displayed appropriate orthogonality, but CsF was preferred because of its higher solubility (Table 1).

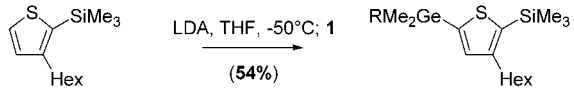
Table 1. Nucleophile Induced *Ipso*-Demetalation of α-germyl and α-silyl-β-hexylthiophenes

substrate	nucleophile	
	K_3PO_4	CsF
2	no cleavage to 110 °C	no cleavage to 110 °C
4	no cleavage to 110 °C	no cleavage to 110 °C
3	partial cleavage at 25 °C, complete cleavage at 60 °C	cleavage at 60 °C
5	cleavage at 60 °C	partial cleavage at 25 °C, complete cleavage at 60 °C

It can be seen from the table that the degree of orthogonality toward reaction with CsF between Ge and Si is not significantly affected by the position of the β-hexyl side chain (cf. **2** vs **3**, and **4** vs **5**, Table 1). However, Tour has shown that *electrophilic ipso*-protodesilylation of α-silyl-β-alkylthiophenes *is* sensitive to regiochemistry, presumably as a result of the inductive stabilization imparted to cationic Wheland-type intermediates by an adjacent alkyl substituent.[11] Furthermore this sensitivity is exacerbated as the oligothiophene chain-length increases.[9] As arylgermanes are more readily cleaved by electrophiles than arylsilanes (as a result of the more powerful β-effect of Ge),[12] we decided that it would be prudent to use 2-germyl-4-hexyl-5-TMS thiophene **6** as our oligomer starter unit to minimize the risk of unwanted electrophile-induced linker cleavage during synthesis.

Thiophene **6** was prepared by reaction of linker model **1** with lithiated thiophene **3** in 54% yield. Here, the TMS protecting group ensures that none of the undesired alternate α-lithiated thiophene is formed and moreover, in the context of SPS, would allow immobilization to be driven to completion by repeating the reaction (Scheme 2).

Scheme 2



3 **6**

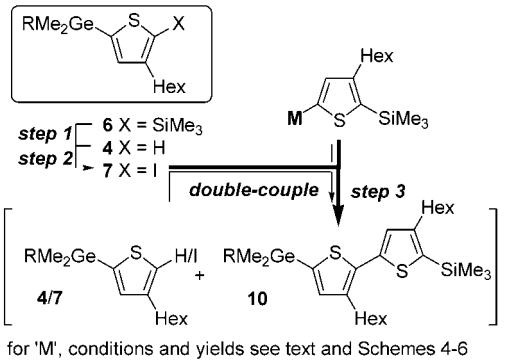
We were now in a position to investigate the three key iterative steps envisaged for building up an oligomer and to check the concept of double-coupling:

(5) The term "double-coupling" is used in the context of solid-phase peptide synthesis for the process whereby a coupling protocol is repeated to drive up the yield of a "difficult" peptide coupling step. Our use of the term is by analogy with this usage. See: Dettin, M.; Pegoraro, S.; Rovero, P.; Bicciato, S.; Bagno, A.; Di Bello, C. *J. Pept. Res.* **1997**, *49*, 103−111.

(6) (a) Spivey, A. C.; Diaper, C. M.; Rudge, A. J. *Chem. Commun.* **1999**, 835−836. (b) Spivey, A. C.; Diaper, C. M.; Adams, H.; Rudge, A. *J. Org. Chem.* **2000**, *65*, 5253−5263.

Step 1: cleavage of the TMS blocking group
Step 2: conversion to an α-iodide coupling precursor
Step 3: cross-coupling of a TMS blocked monomer
Double-coupling: repeat steps 2 and 3 (Scheme 3).

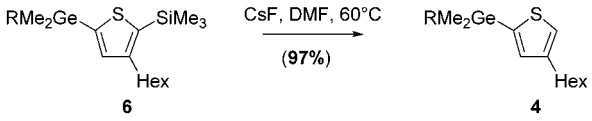
Scheme 3



The role of the TMS group is to block the terminal α-position of the iterated oligomer allowing steps 2 and 3 to be repeated in a double-coupling cycle so as to drive any unreacted iodide and any uniodinated/deiodinated material through to iterated product.

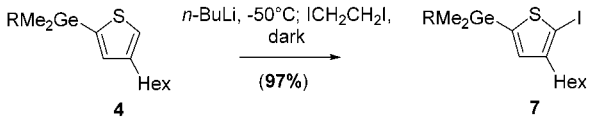
Step 1. As expected from our preliminary studies (Table 1) cleavage of the TMS protecting group in thiophene **6** with CsF was uneventful and gave germylthiophene **4** in 97% yield with no detectable cleavage of the germyl linker (Scheme 4).

Scheme 4



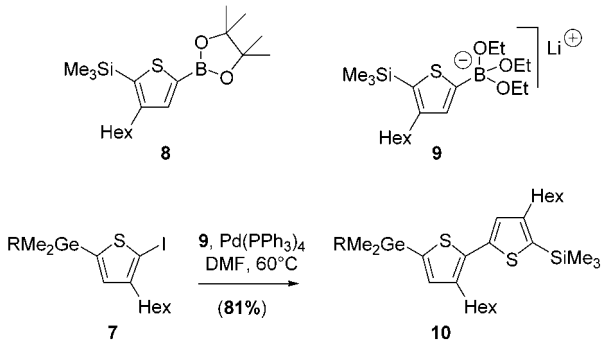
Step 2. α-Iodination of thiophenes is usually accomplished by electrophilic iodination, sometimes with the assistance of mercuration.[13] For our purposes we required conditions that would be compatible with the germyl linker, which is sensitive to electrophilic *ipso*-degermylation. After considerable optimization, the use of excess *n*-BuLi at −50 °C followed by treatment with excess 1,2-diiodoethane in the dark was found to be very efficient in this regard. Conversion of germylthiophene **4** to the corresponding α-iodide **7** under these conditions was achieved in 97% yield (Scheme 5).

Scheme 5



Step 3. Our cross-coupling experiments initially centered on coupling iodothiophene **7** with the readily prepared pinnacolato boronic ester **8**.[14] It became apparent that under a range of standard Suzuki-type cross-coupling conditions employing a variety of bases (e.g., $NaHCO_3$, Cs_2CO_3, NaOAc, Et_3N) and solvents (e.g., THF, toluene, DMF) substantial *ipso*-protodesilylation of the TMS group occurred. To circumvent this problem we developed a "base-free" protocol involving triethylborate salt **9**.[15] This salt is obtained as an easily handled white powder by direct evaporation of volatiles following lithiation/transmetalation of thiophene **3** with *n*-BuLi/$B(OEt)_3$ at −50 °C in THF. Using $Pd(PPh_3)_4$ (<15 mol %) in DMF at 60 °C *in the absence of added base* this salt cross-couples with iodothiophene **7** to give dithiophene **10** in 81% yield. No *ipso*-protodesilylation of the TMS group occurs under these conditions (Scheme 6).

Scheme 6



With the three crucial iterative steps for oligomer extension established we were in a position to investigate whether the TMS group was itself inert to step 2 and therefore sufficiently robust to enable the envisaged double-coupling.

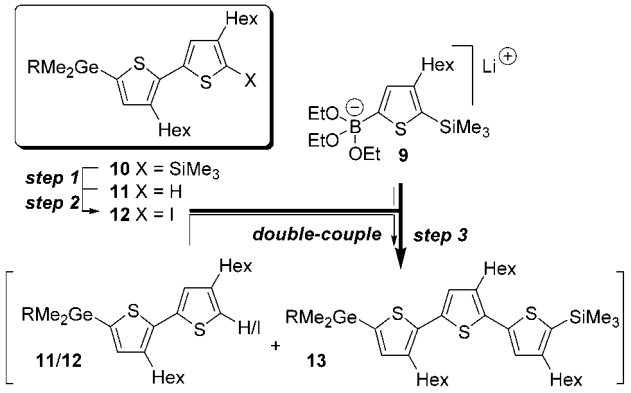
Double-Coupling. Analysis by ^1H NMR of the "crude"[16] reaction mixture following a cross-coupling between iodo-

(7) The term "orthogonal" is used in the context of peptide synthesis to refer to protecting groups (or families thereof) that can be deprotected in the presence of each other. Our use of the term is by analogy with this usage. See: Barany, G.; Merrifield, R. B. *J. Am. Chem. Soc.* **1977**, *99*, 7363−7365.
(8) Li; W.; Maddux, T.; Yu, L. *Macromolecules* **1996**, *29*, 7329−7334.
(9) The trimethylgermyl precursor to chlorogermane **1** (see Supporting Information) is commercially available from AFChemPharm Ltd. See: http://www.afchempharm.co.uk.
(10) Germyl- vs silylalkynes also display orthogonal stability towards nucleophiles; see: Vasella, A.; Cai, C. *Helv. Chim. Acta* **1996**, *79*, 255−268 and references therein.
(11) Tour, J. M.; Wu, R. *Macromolecules* **1992**, *25*, 1901−1907.
(12) Eaborn, C. *J. Organomet. Chem.* **1975**, *100*, 43−57.
(13) See, e.g., ref 4c and references therein.
(14) Boronic ester **8** was prepared by lithiation/transmetalation of thiophene **3** with 2,6-(4-isopropyliden-cyclopentadithiophenyl)-4,4,5,5-tetramethyl-(1,3,2)dioxadiborolane in 52% yield (see Supporting Information). The corresponding boronic acid was unstable in our hands.
(15) We have not rigorously characterized salt **9**, and its structure must therefore be regarded as tentative. For an example of the use of a furan-derived trimethylborate salt in "base-free" cross-coupling, see: Cristofoli, W. A.; Keay, B. A. *Tetrahedron Lett.* **1991**, *32*, 5881−5884.

thiophene **7** and an excess of triethyborate salt **9** (Scheme 6) reveals, in addition to >90% cross-coupled product **10**, small amounts of both unreacted iodothiophene **7** and uniodinated/deiodinated thiophene **4**. Therefore, to validate the concept of double-coupling we subjected this material to a repeat α-iodination/coupling cycle (steps 2 and 3) and reexamined the reaction mixture. Following this simulated double-coupling, byproducts **7** and **8** can no longer be detected by ^{1}H NMR.

A second iteration, including simulated double-coupling, has been performed on dithiophene **10**, yielding trithiophene **13** with analogous results (Scheme 7).

Scheme 7[a]



[a] **Step 1**: CsF, DMF, 60 °C (99%). **Step 2**: *n*-BuLi, -50 °C; ICH_2CH_2I (98%). **Step 3**: **9**, $Pd(PPh_3)_4$, DMF, 60 °C. **Double-couple**: repeat steps 2 and 3 (>90%).

In summary, we have developed the key iterative steps of a new strategy for the synthesis of regioregular oligo-(β-hexylthiophenes) that allows for double-coupling after each iteration to minimize deletion sequences. The success of the double-coupling is contingent upon and highlights the significantly greater stability of (hetero)arylgermanes to nucleophilic conditions relative to the corresponding (hetero)-arylsilanes. This enhanced stability constitutes an important advantage that germanium-based "traceless" linker systems have for SPS relative to their silicon-based counterparts.[17]

We are currently optimizing the strategy for the SPS of high purity oligothiophenes and adapting the concept for the preparation of other oligoheterocycles and derived block co-oligomers.

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Supporting Information Available: Experimental procedures and full characterization for compounds **1**−**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) The reaction mixture was worked up and passed through a short plug of SiO_2, eluting with 9:1 petrol (bp 40−60 °C)/EtOAc. This process removes the "baseline" Pd and excess triethylborate salt **9**.

(17) This feature of germanium-based linker systems has not previously been exploited. Attention has focused on the opportunities that arylgermane-based linkers provide relative to their arylsilane counterparts for more facile electrophilic *ipso*-demetalative cleavage and for employing a wider range of electrophiles for diversity enhancement. See ref 6 and Plunkett M. J.; Ellman, J. A. *J. Org. Chem.* **1997**, *62*, 2885−2893.