First Example of an Enantiospecific sp^3–sp^2 Stille Coupling of a Chiral Allylstannane with Aryl Halides

Rainer Kalkofen, Dieter Hoppe*

Organisch-Chemisches Institut der Westfälischen Wilhelms-Universität Münster, Corrensstraße 40, 48149, Münster, Germany
Fax +49(251)8336531; E-mail: dhoppe@uni-muenster.de

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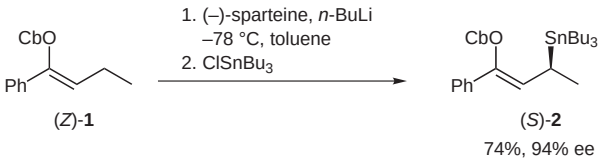
Abstract: A chiral allylic stannane, easily accessible via an enantiotopos differentiating deprotonation of a 1-phenyl-1-alkenyl-carbamate, is coupled with different aryl halides. In this enantiospecific Stille reaction a η^3-bound palladium species is assumed to eliminate either to an arylated 1-alkenyl carbamate or, after migration of the carbamoyloxy group, to a 2-alkenyl carbamate.

Key words: stannanes, C–C coupling, enantioselectivity, allylic compounds, palladium catalysis, asymmetric arylation

The Stille reaction has found numerous applications for the palladium-catalyzed coupling of vinyl- and aryltrialkylstannanes with alkenyl or aryl halides (or the corresponding triflates).[1] In most of the examples, both leaving groups are attached to sp^2-carbon atoms. In few cases, in which sp^3-carbon atoms are involved, the palladium intermediate is unable to undergo β-hydride elimination for constitutional or steric reasons.[2] Few examples of stereospecific Stille-type acylations of chiral benzylic α-alkoxy- or α-aminostannanes with acid chlorides have been described in literature, so far.[3] We now report on the first arylation of an enantioenriched allylstannane, in which its chiral information is almost completely retained.

During our studies on the (–)-sparteine-mediated γ-deprotonation of 1-alkenyl carbamates, we prepared the allylstannane (*S*)-**2** with 94% ee (Scheme 1).[4]

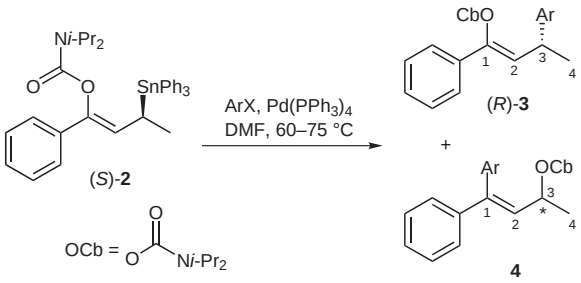


(*Z*)-**1** (*S*)-**2**
74%, 94% ee

Scheme 1 Synthesis of allylic stannane (*S*)-**2**

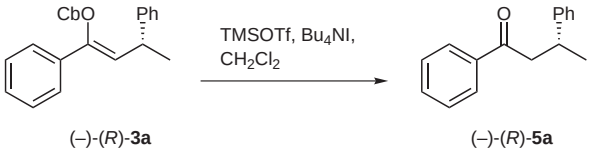
It turned out that **2** could easily be coupled with aryl halides in the presence of $Pd(PPh_3)_4$ in DMF. Variation of the reaction conditions or of the catalyst leads either to decomposition of the starting material or to lower yields.

The coupling reaction leads to the formation of a γ-arylated major product (*R*)-**3** (Scheme 2). In most of the reactions that were carried out the isomeric product **4** was also formed.



Scheme 2 Pd-catalyzed coupling of a chiral allylstannane with aryl halides

The absolute configuration of (*R*)-**3a** was established by transformation into the known ketone (–)-(*R*)-**5a** (Scheme 3).[5]



Scheme 3 Decarbamoylation of (–)-(*R*)-**3a**

One can assume that the reaction proceeds via an η^3–π-palladium complex as reported by Y. Yamamoto.[6,7]

Products **4** have the same enantiomeric purity as the corresponding γ-products **3**, but their absolute configuration, at present, is unknown. This is also true for the product **4a**. Consequently, the precursor for the migration of the OCb group is not the achiral regioisomer **6a**, originating from vinylogous aryl transfer in η^3-complex **B** (Scheme 4, Table 1).[8] The exact mechanism of the coupling reactions still has to be explored. We assume (in analogy to other non-stereogenic Stille couplings) the following catalytic cycle (Scheme 4, Table 1): the aryl halide undergoes an oxidative addition with Pd(0) to give the arylpalladium halide **A**, which reacts with the allylic tin compound (*S*)-**2** with stereoinversion to form the planar-chiral η^3-allylpalladium intermediate **B1**.

Alternatively an η^1-palladium species **B2** might be involved in the course of the reaction. In both possible intermediates the palladium cation is stabilized against racemization by the strongly complexing *N*,*N*-diisopropylcarbamoyloxy group. Intermediates **B1** or **B2** collapse to form the coupling products **3** and **4** with retention of configuration at the allylic moiety with extrusion of Pd(0).

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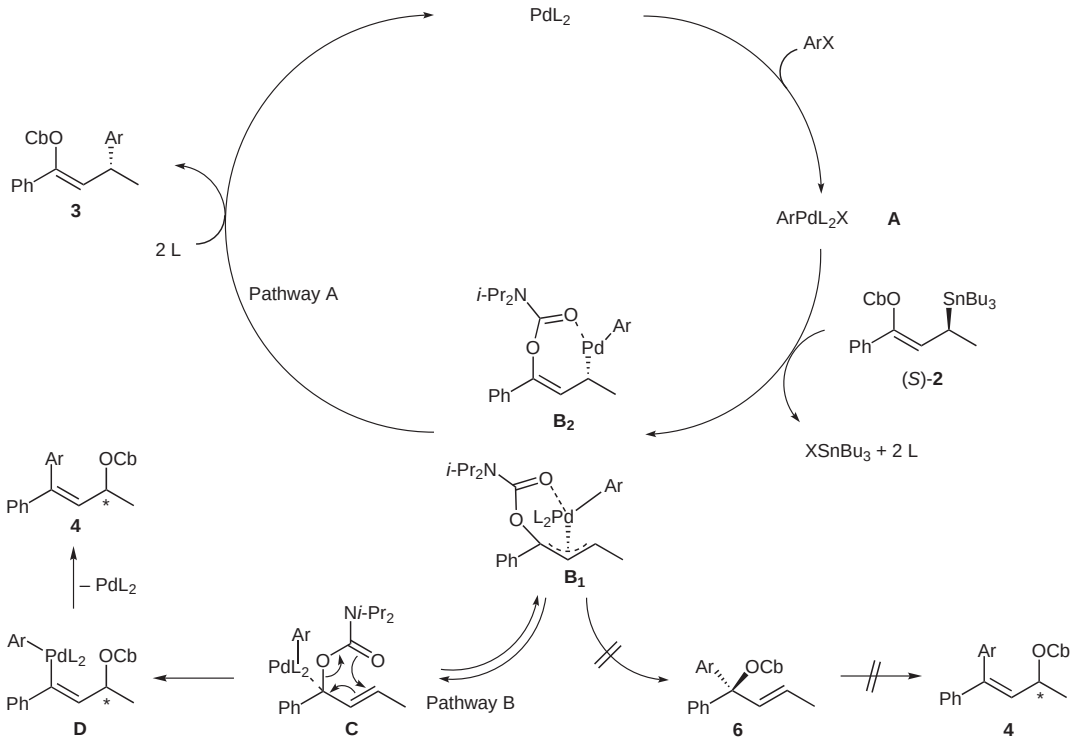
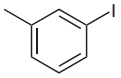
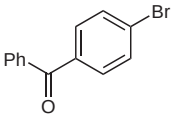
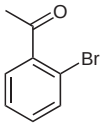
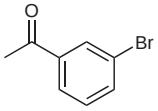
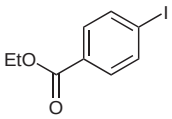


Scheme 4 Proposed mechanism of the enantiospecific Stille coupling with (*S*)-**2**

Table 1 Coupling of (*S*)-**2** (94% ee) with Different Aryl Halides

Entry	ArX	Product **3**/yield (%)	**3**/ee (%)[a]	$[\alpha]_D^{20}$[b]	Product **4**/yield (%)	**4**/ee (%)[a]	$[\alpha]_D^{20}$[b]
1		**3a**/44	94	–64	**4a**/13	94	+44
2		**3b**/41	91	–54	[c]–	–	–
3		**3c**/51	>90	–85	**4c**/27	>90	+102
4		–	[c]–	–	**4d**/67	92	+49
5		**3e**/44	94	–70	**4e**/25	94	+89
6		**3f**/51	90	–60	**4f**/29	90	+85

[a] Determined by chiral HPLC (column: Chira Grom 2).
[b] c = 0.11–0.89, $CHCl_3$.
[c] Not found.

Palladium complex **B** obviously rearranges in part by suprafacial migration of the OCb group to form the chiral vinylpalladium intermediate **D**, in which the aryl residue is transferred by expelling the Pd(0).

In conclusion, the first enantiospecific Stille coupling was developed, overcoming one still remaining limitation of the Stille reaction: coupling of an enantioenriched allylstannane with different aryl halides. In these reactions an almost complete transfer of chirality from the stannane to the allylic carbamate is observed.

Acknowledgment

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References and Notes

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(5) (a) (*R*)-**5a** $[\alpha]_D^{20}$ –11.2 (*c* 0.81, CCl_4); Lit: (–)-(*R*)-**5a** $[\alpha]_D^{20}$ –14.8 (*c* 1.20, CCl_4). (b) Tatemitsu, H.; Ogura, F.; Nakagawa, Y.; Nakagawa, M.; Naemura, K.; Nakazaki, M. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 2473.

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(7) **Typical Procedure.**
$Pd(PPh_3)_4$ (50 mg, 0.04 mmol) and ethyl 4-iodobenzoate (325 mg, 1.00 mmol) were dissolved under argon in 10 mL of DMF at r.t. After 15 min (*S*)-**1** (94% ee, 282 mg, 0.50 mmol) were added and the reaction mixture was heated to 60 °C. After the starting material had been completely consumed (TLC, 12 h) aq sat. NaCl solution (10 mL) was added. The organic layer was separated and the aqueous phase was extracted with Et_2O (3 × 25 mL). The combined organic extracts were dried over $MgSO_4$ and the solvents were evaporated in vacuo. The crude product was purified by flash column chromatography on silica gel (40–63 μm, Et_2O–pentane, 1:3).
Compound (*R*)-**3f**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26, 1.32 (m, 12 H, CH_3-Cb), 1.37 (t, 3 H, H-2′), 1.46 (d, 3 H, H-4), 3.89 (dq, 1 H, H-3); 4.08 (br s, 2 H, CH-Cb), 4.36 (q, 2 H, H-2′), 5.87 (d, 1 H, H-2), 7.15–7.43, 7.96–7.99 (m, 9 H, H-aryl) ppm. Coupling constants: $^3J_{H\text{-}2,H\text{-}3}$ = 12.0 Hz, $^3J_{3\text{-}CH3,H\text{-}3}$ = 9.2 Hz, $^3J_{H\text{-}1',H\text{-}2'}$ = 9.2 Hz. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2 (C-2′), 20.4, 21.4, 21.5 (3-CH_3, CH_3-Cb), 36.6 (C-3), 46.6 (CH-Cb), 60.6 (C-2′), 121.5 (C-2), 124.6, 126.9, 127.9, 128.2, 128.3, 129.7, 135.8 (C-aryl), 146.0 (C-1), 150.7 (C-aryl), 152.4 (C=O-Cb), 166.5 (C=O–O) ppm. IR (film): = 3056, 3030 (Ph–H); 2969, 2923, 2878 (C–H), 2343; 1717, 1697 (C=O), 1656, 1631, 1608, 1575, 1554, 1538, 1502, 1507, 1474, 1456, 1432, 1366, 1306, 1262, 1209, 1183, 1154, 1136, 1119, 1103, 1041, 1026, 892, 854, 756, 704 (Ph–H), 639. MS (Micro-TOF): *m*/*z* = 446.2293 $[M + Na]^+$. R_f = 0.64 (Et_2O–PE = 1:1). Chiral HPLC: t_R = 82.5 min; t_R = 103.4 min (CHIRA-GROM 2, i-PrOH–*n*-hexane = 1:500).
$[\alpha]_D^{20}$ +60 (*c* 0.53, $CHCl_3$, 90% ee, 3*R*). Anal. Calcd for $C_{26}H_{33}NO_4$ (423.24): C, 73.73; H, 7.85; N, 3.31. Found: C, 73.62; H, 7.99; N, 3.17.
Compound (+)-**4f**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (t, 12 H, CH_3-Cb), 1.32 (d, 3 H, H-4), 1.39 (t, 3 H, H-2′), 3.90 (br s, 2 H, CH-Cb), 4.39 (q, 2 H, H-2′), 5.33 (dq, 1 H, H-3), 6.11 (d, 1 H, H-2), 7.19–7.34, 8.05–8.08 (m, 9 H, H-aryl) ppm. Coupling constants: $^3J_{H\text{-}2,H\text{-}3}$ = 12.0 Hz, $^3J_{H\text{-}3,H\text{-}4}$ = 8.8 Hz, $^3J_{H\text{-}1',H\text{-}2'}$ = 9.2 Hz. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.7 (C-2′), 15.6 (C-4), 21.7 (CH_3-Cb), 46.2 (CH-Cb), 61.3 (C-2′), 69.7 (C-3), 127.8, 128.1, 128.6, 130.0, 130.7, 139.8, 141.6, 142.3, 143.3, 144.4 (C-aryl), 144.4 (C-1), 155.3 (C=O-Cb), 166.9 (C=O) ppm. IR (film): 3082, 3056 (Ph–H), 2969, 2926, 2901, 2873 (C–H), 1717, 1686 (C=O), 1604, 1439, 1400, 1365, 1273, 1213, 1178, 1134, 1095, 1017, 913, 765, 708 (Ph–H) 695 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{26}H_{33}NO_4$: 446.2302 $[M + Na]^+$; found: 446.2285. R_f = 0.65 (Et_2O–PE = 1:1). Chiral HPLC: t_R = 10.4 min; t_R = 12.8 min (CHIRA-GROM 2, i-PrOH–*n*-hexane = 1:100). $[\alpha]_D^{20}$ +85 (*c* 0.51, $CHCl_3$, 90% ee). Anal. Calcd for $C_{26}H_{33}NO_4$ (423.24): C, 73.73; H, 7.85; N, 3.31. Found: C, 73.75; H, 7.92; N, 3.14.

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