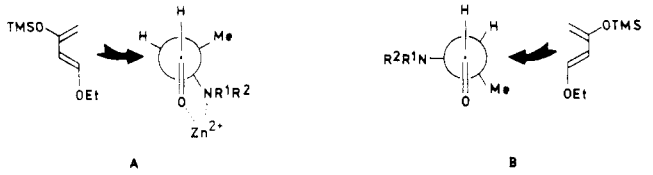
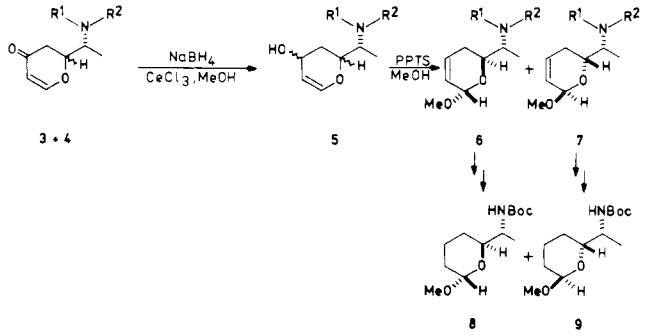


Figure 1.

Scheme II



action rises with the steric hindrance of the blocking groups.

The mixtures of adducts **3** and **4** could not be easily separated; they were reduced by means of Luche's method[6] to afford corresponding mixtures of alcohols **5** (Scheme II). Ferrier rearrangement[7] in conjunction with cis → trans isomerization at the anomeric carbon[8] afforded a mixture of adducts **6** and **7**. The absolute configurations of these 5,6-dihydro-2*H*-pyrans were established by means of ^1H and ^{13}C NMR spectroscopy.[9,10] Independently, they were transformed into the known compounds **8** and **9**.[2,10]

The presented results demonstrate that it is possible to control the stereochemistry of Lewis acid catalyzed (4 + 2) cycloaddition with α-amino aldehydes as heterodienophiles, by means of changing the N-protecting groups. The inversion of "natural" syn selectivity[2] can be achieved by the removal of both amino protons.

The diastereoselectivity of the studied reaction depends on the solvent and catalyst concentration and was not optimized toward these parameters.[11] Enlargement upon these findings and the application of the presented approach to the total synthesis of complex amino sugars are matters of continuing interest in this laboratory.

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Registry No. **1**, 54125-02-9; **2a**, 82353-56-8; **2b**, 82353-55-7; **2c**, 120294-57-7; **2d**, 120205-96-1; **2e**, 120205-97-2; **2f**, 120205-98-3; **3a**, 120205-99-4; **3b**, 120206-00-0; **3c**, 120206-01-1; **3d**, 120206-02-2; **3e**, 120229-29-0; **3f**, 120206-03-3; **4a**, 120206-04-4; **4b**, 120206-05-5; **4c**, 120206-06-6; **4d**, 120206-07-7; **4e**, 120206-08-8; **4f**, 120206-09-9; **5a**, 120206-10-2; **5b**, 120206-11-3; **5c**, 120206-12-4; **5d**, 120206-13-5; **5e**, 120206-14-6; **5f**, 120229-30-3; **6a**, 120294-58-8; **6b**, 120294-59-9; **6c**, 120294-60-2; **6d**, 120206-15-7; **6e**, 120206-16-8; **6f**, 120328-36-1; **7a**, 120294-61-3; **7b**, 120294-62-4; **7c**, 120294-63-5; **7d**, 120294-64-6; **7e**, 120294-65-7; **7f**, 120206-17-9.

(6) Luche, J. L.; Gemal, A. L. *J. Am. Chem. Soc.* **1979**, *101*, 5848.
(7) Ferrier, R. J. *J. Chem. Soc.* **1964**, 5443.
(8) Jurczak, J.; Bauer, T.; Gołebiowski, A. *Bull. Pol. Ac.: Chem.* **1985**, *33*, 397.
(9) Chmielewski, M.; Konował, A.; Zamojski, A. *Carbohydr. Res.* **1979**, *70*, 275.
(10) Gołebiowski, A. Ph.D. Thesis; Institute of Organic Chemistry, Polish Academy of Sciences, Warszawa, 1987.
(11) Influence of the solvent on the stereochemical course of the similar reaction was studied: Garner, P.; Ramakanth, S. *J. Org. Chem.* **1986**, *51*, 2609.

Palladium-Catalyzed Cross-Coupling of Organostannanes with Sulfonyl Chlorides: A Simple Synthesis of Sulfones[1]

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Summary: The palladium-catalyzed cross-coupling reaction between aryl- and alkylsulfonyl chlorides and substituted vinyl- and allylstannanes proceeds smoothly to provide good yields of sulfones and tolerates a wide variety of functionalities.

Sir: Sulfones are gaining attention as synthetic intermediates and also as medicinally important molecules.[2] Frequently used methods for the preparation of sulfones are the sulfonylation of aromatic hydrocarbons in the presence of a Lewis acid, oxidation of sulfides with peracids or with oxone, and nucleophilic substitution with sulfenic acid salts.[3] Although there are a number of methods available for the preparation of vinyl and allyl sulfones, simple one-step procedures are scarce.[4]

Transition metal catalyzed coupling reactions involving organostannanes have been widely used in the carbon–carbon bond formation.[5] Coupling partners include acyl, aryl, vinyl, and allyl halides, as well as aryl and vinyl triflates.[5,6] The palladium-catalyzed cross-coupling reactions of organostannanes proceed under mild conditions to provide excellent yields of coupling products and tolerate a wide variety of functionalities. However, to date, analogous palladium-catalyzed coupling of organostannanes with sulfonyl chlorides to form sulfones has not been documented. We have found that alkyl- and aryl-

(1) Contribution No. 768 from the Institute of Organic Chemistry.
(2) Trost, B. M. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 107.
(3) Durst, T. *Comprehensive Organic Chemistry, The Synthesis and Reactions of Organic Compounds*; Paragon Press: New York, 1979; Vol. 3, Chapter 11.8, p 171.
(4) Durst, T. *Comprehensive Organic Chemistry, The Synthesis and Reactions of Organic Compounds*; Paragon Press: New York, 1979; Vol. 3, Chapter 11.9, p 196.
(5) (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508 and references therein. (b) Stille, J. K. *Pure Appl. Chem.* **1985**, *57*, 1771.
(6) (a) Krolski, M. E.; Renaldo, A. F.; Rudisill, D. E.; Stille, J. K. *J. Org. Chem.* **1988**, *53*, 1170. (b) Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478.

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Table I. Coupling of RSO_2Cl with Bu_3SnR^1 According to Eq 1[a]

entry	R	R^1	reaction time	yield of RSO_2R^1,[b] %
1	Np[c]	(*E*)-C_6H_5CH=CH	15 min	0[d]
2	Np[c]	(*E*)-C_6H_5CH=CH	15 min	70
3	Me	(*E*)-C_6H_5CH=CH	15 min	90
4	*p*-MeC_6H_4	(*E*)-C_6H_5CH=CH	15 min	77
5	*p*-ClC_6H_4	(*E*)-C_6H_5CH=CH	15 min	75
6	*m*-$HOOCC_6H_4$[e]	(*E*)-C_6H_5CH=CH	15 min	75
7	Np[c]	(*E*)-$C_6H_{13}CH$=CH	30 min	70
8	*p*-$MeOC_6H_4$	(*E*)-$C_6H_{13}CH$=CH	30 min	87
9	*p*-$MeOC_6H_4$	(*E*)-$THPOCH_2CH$=CH	30 min	90
10	Np[c]	(*E*)-$THPOCH_2CH$=CH	30 min	85
11	Np[c]	$THPOCH_2CH$=CH[f]	30 min	75[g]
12	*p*-MeC_6H_4	(*E*)-EtOOCCH=CH	30 min	68
13	*p*-MeC_6H_4	(*Z*)-EtOOCCH=CH	30 min	64[g]
14	Np[c]	(*E*)-CH_3CH=$CHCH_2$	3 h	60[h]
15	*p*-$MeOC_6H_4$	(*E*)-CH_3CH=$CHCH_2$	3 h	60
16	*p*-MeC_6H_4	*p*-$MeOC_6H_4CH_2$	12 h	57[i]
17	Np[c]	C_6H_5C≡C	15 min	0[j]

[a] All reactions were carried on 1 mmol of sulfonyl chlorides with 1.1 mmol of the tin reagent in the presence of 1 mol % of the catalyst 1 at 65–70 °C. [b] Isolated yields. Satisfactory spectral and analytical data were obtained on all products. [c] Np represents 2-naphthalene. [d] No catalyst was used. [e] Product was converted to the methyl ester with diazomethane to facilitate the purification. [f] A 1:1 *E*/*Z* mixture. [g] Only (*E*)-sulfone was formed. [h] 3-(1-Butenyl) 2-naphthyl sulfone was formed. [i] Dioxane was used as solvent. [j] 1,4-Diphenyl-1,3-butadiyne was isolated in 70% yield.

sulfonyl chlorides readily undergo palladium-catalyzed coupling with organostannanes to form sulfones (eq 1), and wish to report our initial work of this investigation.

$$RSO_2Cl + Bu_3SnR^1 \xrightarrow[THF]{(Ph_3P)_4Pd\ (1)} RSO_2R^1 + Bu_3SnCl \quad (1)$$

The reaction between (*E*)-styryltributylstannane and 2-naphthalenesulfonyl chloride in the presence of 1 mol % of tetrakis(triphenylphosphine)palladium(0), 1, proceeded smoothly to provide the cross-coupled product, 2-naphthyl (*E*)-styryl sulfone (Table I, entry 2), within 15 min in THF at 65–70 °C. None of the product was formed when the above reaction was run simultaneously without the catalyst (entry 1).[7] (*E*)-Styryltributylstannane reacted smoothly with a variety of sulfonyl chlorides to provide the expected sulfones in good yield (entries 2–6). Aromatic halogen and carboxylic acid groups on the sulfonyl chloride partner are tolerated under the reaction conditions (entries 5 and 6). Attempts to couple *o*- and *m*-nitrobenzenesulfonyl chlorides with (*E*)-styryltributylstannane were unsuccessful. The coupling proceeded smoothly to furnish desired sulfones with a variety of substituted vinylstannanes (entries 7–13). Lower yields of the sulfones were obtained with ethyl 3-(tributylstannyl)propenoates (entries 12 and 13). Crotyltributylstannane reacted to provide 3-(1-butenyl) 2-naphthyl sulfone and 3-(1-butenyl) *p*-methoxyphenyl sulfone (entries 14 and 15), formed by allylic transposition. Similar allylic transposition has been observed in the palladium-catalyzed coupling reactions of allylstannanes with allyl and vinyl iodides and acid chlorides.[8,9a] The coupling between (*p*-methoxybenzyl)tributylstannane and *p*-toluenesulfonyl chloride provided the corresponding sulfone; however, the reaction required a longer period of time and dioxane as solvent (entry 16). Unsubstituted vinyl- and allylstannanes and phenyltributylstannane did not provide the corresponding sulfones with sulfonyl chlorides.

The cross-coupling reaction was observed to occur with retention of the double-bond geometry for (*E*)-vinylstannanes, as usually observed. When a mixture of (*E*)- and (*Z*)-[3-[(tetrahydro-2*H*-pyran-2-yl)oxy]-1-propenyl]tributylstannane (*E*/*Z* ratio of 1:1, entry 11) was reacted with 2-naphthalenesulfonyl chloride, only the (*E*)-sulfone was formed. In a similar manner, (*Z*)-ethyl 3-(tributylstannyl)propenoate reacted to provide exclusively (*E*)-sulfone (entry 13). It has been shown that in the palladium-catalyzed coupling reaction between acyl chlorides and (*Z*)-vinylstannanes the transmetalation of vinylstannanes occurs with the retention of configuration across the double bond and the product (*Z*)-ketone isomerizes to thermodynamically more stable *E* isomer under the reaction conditions.[9] Similar isomerization is presumed to be taking place with initially formed (*Z*)-sulfones from (*Z*)-vinylstannanes under the reaction conditions.

In some cases, efficient synthesis of sulfones by this method is beset by side reactions, such as the self-coupling of the tin reagents, and desulfonylation. The reaction between 2-naphthalenesulfonyl chloride and (phenylethynyl)tributylstannane provided the self-coupling product, 1,4-diphenyl-1,3-butadiyne (entry 17) in 70% yield. Similar results were obtained with *p*-toluene-, 4-methoxybenzene- and methanesulfonyl chlorides. (*E*)-Styryltributylstannane gave a small amount (5%) of the self-coupling product, 1,4-diphenyl-1,3-butadiene, whereas ethyl 3-(tributylstannyl)propenoates provided variable amounts (5–25%) of diethyl 1,3-butadiene-1,4-dicarboxylate at different reaction temperatures. The presence of the sulfonyl chloride and the catalyst was necessary for the self-coupling to occur. It has been previously demonstrated that the oxidative addition products of arylsulfonyl chlorides to metal complexes generate aryl chloride with sulfur dioxide extrusion under thermal decomposition conditions.[10–12] Only trace amounts of products due to desulfonylation were formed.

The formation of sulfones from the cross-coupling of sulfonyl chlorides and organostannanes in the presence of the palladium catalyst 1 can be explained by analogy with the formation of ketones from acyl chlorides.[9a] Three key steps involved in the formation of ketones from acyl chlorides and organostannanes in the presence of a pal-

(7) After extended period of time some product was formed.
(8) Godschalx, J.; Stille, J. K. *Tetrahedron Lett.* **1980**, *21*, 2599.
(9) (a) Labadie, J. W.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 6129. (b) Goure, W. F.; Wright, M. E.; Davis, P. D.; Labadie, S. S.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 6417.
(10) (a) Blum, J.; Scharf, G. *J. Org. Chem.* **1970**, *35*, 1895. (b) Collman, J. P.; Roper, W. R. *J. Am. Chem. Soc.* **1966**, *88*, 180. (c) Cook, C. D.; Jauhal, G. S. *Can. J. Chem.* **1967**, *45*, 301.
(11) Blum, J. *Tetrahedron Lett.* **1966**, 3041.
(12) Garves, K. *J. Org. Chem.* **1970**, *35*, 3273.

ladium catalyst are (1) oxidative addition of acyl chlorides to palladium(0), (2) transmetalation of organostannane, and (3) reductive elimination of the product. The oxidative addition of arylsulfonyl chlorides to platinum(0), rhodium(I), and palladium(II) complexes is well documented.[10-12] Although there is no documentation on the transmetalation and subsequent reductive elimination with the formation of a C–S bond, these same intermediate steps could be proposed for the catalytic cycle. The mechanism for the self-coupling of organostannanes is not yet clear.

The following procedure for the coupling of (*E*)-styryltributylstannane with *p*-toluenesulfonyl chloride is representative. To a solution of *p*-toluenesulfonyl chloride (200 mg, 1.0 mmol) in 5 mL of dry THF was added (*E*)-styryltributylstannane (430 mg, 1.1 mmol) followed by tetrakis(triphenylphosphine)palladium(0), **1** (12 mg, 1.0 mol %). The resulting pale yellow solution was heated at 65–70 °C for 15 min with stirring. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and treated with an excess of aqueous KF for 2–3 h with vigorous stirring. The precipitated tin fluoride complex was removed by filtration and was washed well with ethyl acetate. The organic layer was separated, washed with brine, and dried (Na_2SO_4). The solvent was removed on a rotary evaporator, and the residue was purified by flash chromatography to give (*E*)-styryl *p*-toluyl sulfone (0.19 g, 77%): mp 121–122 °C (hexane/EtOAc, lit.[13] mp 121–122 °C).

In summary, a general, single-step method for the preparation of vinyl- and allylsulfones was developed. This palladium-catalyzed cross-coupling reaction proceeds to provide good to excellent yields of sulfones and is highly catalytic. The reaction, however, is limited to the substituted alkenyl- and allylstannanes. The palladium-catalyzed self-coupling of the organostannanes, which has not been previously reported, is noteworthy and further investigation of this aspect is under way. In this paper, we have shown that the palladium-catalyzed coupling reactions of substituted vinyl- and allylstannanes can be applied in the C–S bond formation, as well.

(13) Truce, W. E.; Simms, J. A.; Hill, H. E. *J. Am. Chem. Soc.* **1953**, *75*, 5411.

Total Synthesis of K-13

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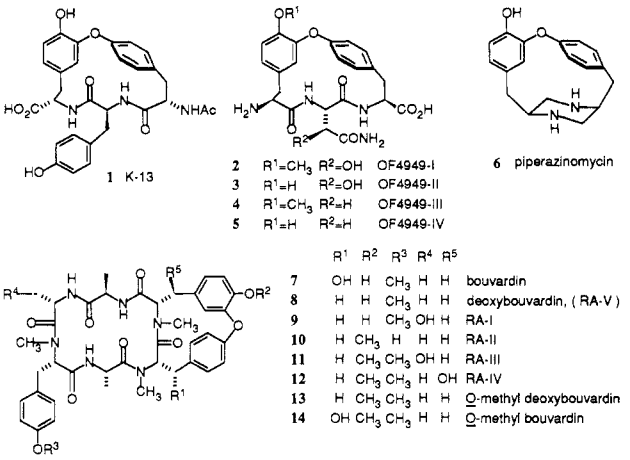
Summary: A total synthesis of K-13 (1), an isodityrosine-derived cyclic tripeptide possessing potent noncompetitive angiotensin I converting enzyme inhibitory activity, is detailed.

Sir: K-13 (1), an isodityrosine-derived cyclic tripeptide isolated from *Micromonospora halophytica* subsp. *exilisia K-13* and identified by spectroscopic and chemical degradative studies,[1] has been shown to be a potent, noncompetitive inhibitor of angiotensin I converting enzyme (I_{50} = 0.17 μg/mL, K_i = 0.35 μM) and a weak inhibitor of aminopeptidase B.[2] Consequently, K-13 represents the newest addition to a class of biologically active isodityrosine-derived[3] cyclic peptides now including OF4949-I–OF4949-IV (**2–5**),[4] piperazinomycin (**6**),[5] and a growing class of bicyclic hexapeptide antitumor–antibiotics **7–14**.[6]



(1) Kase, H.; Kaneko, M.; Yamada, K. *J. Antibiot.* **1987**, *40*, 450.

(2) Yasuzawa, T.; Shirahata, K.; Sano, H. *J. Antibiot.* **1987**, *40*, 455.

(3) Isodityrosine: (a) Fry, S. C. *Biochem. J.* **1982**, *204*, 449. (b) Cooper, J. B.; Varner, J. E. *Biochem. Biophys. Res. Commun.* **1983**, *112*, 161.

(4) OF4949-I–OF4949-IV. Fermentation, isolation, and characterization: (a) Sano, S.; Ikai, K.; Kuroda, H.; Nakamura, T.; Obayashi, A.; Ezure, Y.; Enomoto, H. *J. Antibiot.* **1986**, *39*, 1674. Structure elucidation: (b) Sano, S.; Ikai, K.; Katayama, K.; Takesako, K.; Nakamura, T.; Obayashi, A.; Ezure, Y.; Enomoto, H. *J. Antibiot.* **1986**, *39*, 1685. Biosynthesis: (c) Sano, S.; Ueno, M.; Katayama, K.; Nakamura, T.; Obayashi, A. *J. Antibiot.* **1986**, *39*, 1697. Total synthesis: (d) Nishiyama, S.; Suzuki, Y.; Yamamura, S. *Tetrahedron Lett.* **1988**, *29*, 559. (e) Schmidt, U.; Weller, D.; Holder, A.; Lieberknecht, A. *Tetrahedron Lett.* **1988**, *29*, 3227.

(5) Piperazinomycin. Fermentation, isolation, characterization, and biological properties: Tamai, S.; Kaneda, M.; Nakamura, S. *J. Antibiot.* **1982**, *35*, 1130. X-ray structure determination: Kaneda, M.; Tamai, S.; Nakamura, S.; Hirata, T.; Kushi, Y.; Suga, T. *J. Antibiot.* **1982**, *35*, 1137. Total synthesis: Nishiyama, S.; Nakamura, K.; Suzuki, Y.; Yamamura, S. *Tetrahedron Lett.* **1986**, *27*, 4481. Synthetic studies: Jung, M. E.; Rohloff, J. C. *J. Org. Chem.* **1985**, *50*, 4909.

(6) (a) Jolad, S. D.; Hoffmann, J. J.; Torrance, S. J.; Wiedhopf, R. M.; Cole, J. R.; Arora, S. K.; Bates, R. B.; Gargiulo, R. L.; Kriek, G. R. *J. Am. Chem. Soc.* **1977**, *99*, 8040. (b) Itokawa, H.; Takeya, K.; Mori, N.; Sonobe, T. ; Mihashi, S.; Hamanaka, T. *Chem. Pharm. Bull.* **1986**, *34*, 3762. Itokawa, H.; Takeya, K.; Mihara, K.; Mori, N.; Hamanaka, T.; Sonobe, T.; Iitaka, Y. *Chem. Pharm. Bull.* **1983**, *31*, 1424. Itokawa, H.; Takeya, K.; Mori, N.; Kidokoro, S.; Yamamoto, H. *Planta Med.* **1984**, *51*, 313. (c) Natural and synthetic derivatives of RA bicyclic hexapeptides: Itokawa, H.; Takeya, K.; Mori, N.; Sonobe, T.; Serisawa, N.; Hamanaka, T.; Mihashi, S. *Chem. Pharm. Bull.* **1984**, *32*, 3216. Itokawa, H.; Takeya, K.; Mori, N.; Takanashi, M.; Yamamoto, H.; Sonobe, T.; Kidokoro, S. *Gann.* **1984**, *75*, 929. Itokawa, H.; Takeya, K.; Mori, N.; Hamanaka, T.; Sonobe, T.; Mihara, K. *Chem. Pharm. Bull.* **1984**, *32*, 284. (d) Total synthesis: Inaba, T.; Umezawa, I.; Yuasa, M.; Inoue, T.; Mihashi, S.; Itokawa, H.; Ogura, K. *J. Org. Chem.* **1987**, *52*, 2957. (e) Synthetic studies and key partial structures: Bates, R. B.; Gin, S. L.; Hassen, M. A.; Hruby, V. J.; Janda, K. D.; Kreik, G. R.; Michaud, J.-P.; Vine, D. B. *Heterocycles* **1984**, *22*, 785. Boger, D. L.; Yohannes, D. *J. Org. Chem.* **1988**, *53*, 487. Inoue, T.; Naitoh, K.; Kosemura, S.; Umezawa, I.; Sonobe, T.; Serizawa, N.; Mori, N.; Itokawa, H. *Heterocycles* **1983**, *20*, 397.

0022-3263/89/1954-2498$01.50/0