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A ONE-POT SYNTHESIS OF CONJUGATED DIENYNES BY PALLADIUM-MEDIATED THREE COMPONENT CROSS-COUPLING REACTION

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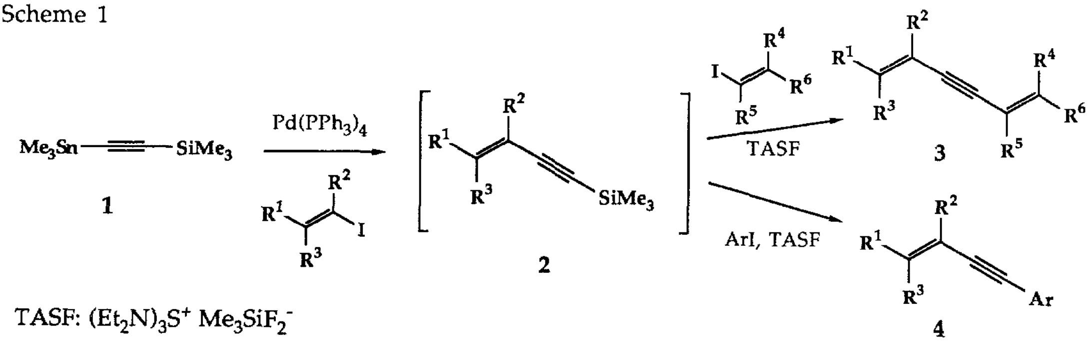
Palladium-catalyzed one-pot sequential reaction of $Me_3SnC{\equiv}CSiMe_3$ *first with an alkenyl iodide* R^1I *and secondly with another alkenyl (or aryl) iodide* R^2I *in the presence of newly added* $(Et_2N)_3S^+\ Me_3SiF_2^-$ *affords conjugated dienynes* $R^1\text{-}C{\equiv}C\text{-}R^2$ *with high stereospecificity.*

Stereo-defined conjugated polyenynes containing an internal carbon-carbon triple bond unit are widely distributed in nature and show interesting biological activities.[1] Although many stereospecific or stereoselective synthetic methods for conjugated polyenynes have been developed,[2] the one which involve direct coupling of two alkenyl units with an acetylene moiety should be the most straightforward for the construction of an unsymmetrical dienyne unit. For the coupling reaction a number of transition metal-catalyzed cross-coupling reactions are applicable, which utilize the stereo-defined alkenyl halides and alkynyl metals of a magnesium,[3] boron,[4] copper,[5] and tin.[6] We recently described a general approach to conjugated dienes using cross-coupling reaction of alkenylsilanes with alkenyl iodides mediated by fluoride ion and palladium catalyst.[7] The efficacy of this method and the increasing interest in conjugated polyenynes prompted us to extend the silicon-based cross-coupling reaction to the synthesis of this class of compounds.

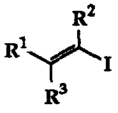
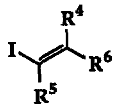
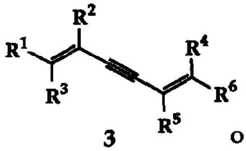
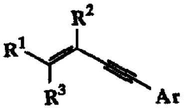
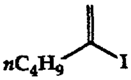
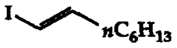
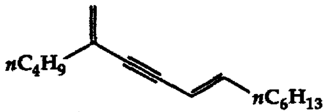
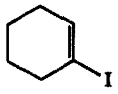
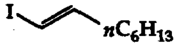
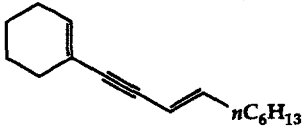
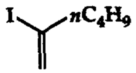
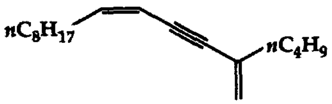
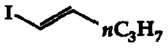
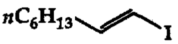
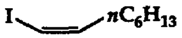
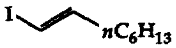
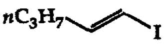
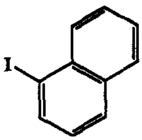
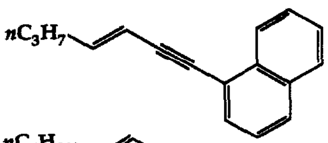
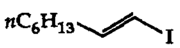
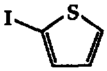
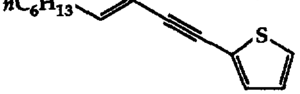
Reported herein is a one-pot synthesis of strereo-defined 1,5-dien-3-ynes. Basic concept of our reaction is illustrated in Scheme 1. The process involves the palladium catalyzed reaction of an

Scheme 1



TASF: $(Et_2N)_3S^+\ Me_3SiF_2^-$

Table 1 One-Pot Reaction of **1** with Two Different Iodides to Give **3** or **4**

run^a				Yield %^{b}
			 3 or  4	
1				80
2				72
3				85
4				58
5				68
6				70
7				47
8^c				63
9^c				55

a) Unless otherwise stated, all the reactions were carried out in THF at 50°C using 1.2 mol of **1**, 2.4 mol of TASF and 5 mol% of $Pd(PPh_3)_4$.

b) Isolated yields.

c) The reaction was carried out in DMF in lieu of THF.

alkenyl iodide with the carbon-tin bond of trimethylstannyl(trimethylsilyl)ethyne (1).[6] The trimethylsilylbutenyne intermediate **2** is then allowed to undergo cross-coupling reaction with another alkenyl iodide accompanied by tris(diethylamino)sulfonium trimethyldifluorosilicate (TASF)[8] in the presence of the same palladium catalyst to give rise to the desired conjugated dienes **3**.

The procedure for the preparation of (8Z)-5-methylene-8-heptadecen-6-yne is representative. Trimethylstannyl(trimethylsilyl)ethyne (**1**) (313 mg, 1.2 mmol) was added to a THF (10 ml) solution of (Z)-1-iodo-1-decene (266 mg, 1.0 mmol) and palladium tetrakis(triphenylphosphine)[9] (58 mg, 0.05 mmol, 5 mol%) under a nitrogen atmosphere at ambient temperature. The mixture was then stirred at 50°C and the reaction was monitored by GLC until the iodooctene was consumed (1.5 h). 2-Iodo-1-hexene (210 mg, 1.0 mmol) and a THF solution of TASF (0.69 M, 3.5 ml, 2.4 mmol)[10] were added at -78°C. The mixture was slowly warmed to ambient temperature, allowed to react for 2 h at 50°C, then cooled to room temperature, and finally was quenched with aq sodium bicarbonate. Workup followed by purification by column chromatography (silica gel, hexane) afforded the desired product (202 mg, 82% yield),[11] the stereoisomeric purity of which was shown to be more than 95% by GLC assay (OV-1 capillary column, 25 m).

The one-pot reaction was applied to various alkenyl iodides and aryl iodides. The results summarized in Table 1 show the following salient features of the novel process. *Palladium(0) catalyst* can be applied in a single flask to double coupling reactions based on two different Group 14 elements under strickt reactivity control. The reaction proceeds with retention of the double bond geometry of the alkenyl iodides as is often the case with the coupling reaction of organotin and organosilicon compounds. Thus, the synthesis of conjugated (*E*,*E*)-, (*E*,*Z*)- and even (*Z*,*Z*)-1,5-dien-3-ynes of high stereoisomeric purity is readily achieved (runs 5, 6, and 7). Taking advantage of the reactivity of alkenyl iodide over allylic carboxylate, we could synthesize (2*E*,6*E*)-1-acetoxy-2,6-decadiene-4-yne,[12] a naturally occuring polyenyne isolated from *Grindelia humilis* Hook (run 4).[13]

When aryl iodides were employed as the second coupling partner, DMF was proved to be the best solvent (runs 8 and 9). In THF, the second coupling reaction turned out to be sluggish. For example, *the reaction of* **1** *in THF with (E)-1-iodo-1-heptene as the first coupling* partner and 1-iodonaphthalene as the second one gava (*E*)-3-hepten-1-yne as a sole isolable product.

The palladium catalyzed three component coupling reaction of trimethylstannyl(trimethylsilyl)-ethyne (**1**) with two different alkenyl iodides can be effected sequentially in one-pot, and a 1,5-dien-3-yne structure is now readily constructed with high stereospecificity. The procedure should find wide application to the synthesis of a large array of naturally occuring substance having the conjugated dienyne system.

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8 When the fluoride reagent TASF is added with the first alkenyl iodide for the first step of the coupling reaction, C-C bond formation takes place at both terminal carbons of **1** to give a symmetric dienyne. For example, when **1** (1.1 mmol) was allowed to react with (*E*)-1-iodo-1-octene (1.0 mmol) under the influence of TASF (1.0 mmol) and $Pd(PPh_3)_4$ catalyst, (7*E*,11*E*)-7,11-octadecadien-9-yne (0.38 mmol) was obtained.

9 For the success of the reaction, the kind of the palladium catalyst is critical. $PdCl_2(PPh_3)_2$ and $PdCl_2(MeCN)_2$ catalyzed reactions of **1** with 1-iodocyclohexene as the first iodide and (*E*)-1-iodo-1-octene as the second one in THF gave a relatively large amount of 1-cyclohexenylethyne which was presumably derived from protodesilylation of an intermediate 1-[(trimethylsilyl)-ethynyl]cyclohexene in addition to the expected sequentially coupled product (7*E*)-10-(1-cyclohexenyl)-7-decen-9-yne. The use of $(\eta^3\text{-}C_3H_5PdCl)_2$ as the catalyst, which was effective for the TASF-mediated reaction of alkynyltrimethylsilane with alkenyl halides,[7a] resulted in extensive homo-coupling of alkynyltin reagent to yield 1,4-bis(trimethylsilyl)-1,3-butadiyne. The highest yields of the sequentially coupled product was obtained with $Pd(PPh_3)_4$ catalyst (run 1 of Table 1).

10 The reaction with tetrabutylammonium fluoride (purchased form Aldrich) used in place of TASF afforded a substantial quantity of protodesilylated product of intermediate **2** possibly owing to hydrate contamination.

11 ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (t, J = 7.0 Hz, 3 H), 0.92 (t, J = 7.3 Hz, 3 H), 1.20-1.46 (m, 14 H), 1.49-1.48 (m, 2 H), 2.19 (t, J = 7.4 Hz, 2 H, $C_{(4)}$-H_2), 2.32 (ddt, J = 7.4, 7.4, 1.3 Hz, 2 H, $C_{(10)}$-H_2), 5.21 (m, 1 H, vinylic), 5.28 (d, J = 2.0 Hz, 1 H, vinylic), 5.57 (dt, J = 10.7, 1.3 Hz, 1 H, $C_{(8)}$-H), 5.91 (dt, J = 10.7, 7.4 Hz, 1 H, $C_{(9)}$-H); IR (neat) 3125, 2200, 1610, 890 cm^{-1}. Anal. Calcd for $C_{18}H_{30}$: C, 87.73; H, 12.27. Found: C, 87.81; H, 12.15.

12 The ^{1}H NMR and IR spectra were identical to those reported.[13b]

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