Pergamon

Tetrahedron Letters 43 (2002) 1261–1264

TETRAHEDRON LETTERS

Preparation and Stille cross-coupling reaction of the first organotin reagents of azulenes. An efficient Pd(0)-catalyzed synthesis of 6-aryl- and biazulenes

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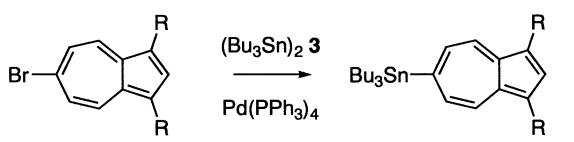
Received 8 November 2001; revised 3 December 2001; accepted 7 December 2001

Abstract—The first versatile organometallic reagents of azulenes, 6-(tri-*n*-butylstannyl)azulenes, have been prepared by a Pd(0)-catalyzed direct stannylation of 6-bromoazulenes with bis(tri-*n*-butyltin). We demonstrate herein the utility of the reagents in the Stille cross-coupling reaction with aryl and azulenyl halides to afford 6-aryl- and biazulenes in good yield.

Palladium-catalyzed cross-coupling reaction has become a widely used method of the carbon–carbon bond formation in modern organic synthesis.[1] Several applications of the transition metal-catalyzed reaction in the chemistry of azulenes have also appeared in the literature, e.g. palladium-catalyzed vinylation,[2] arylation,[3] and ethynylation[4] of haloazulenes. However, the lack of an organometallic reagent of the azulene itself imposes restrictions on the versatile transition metal-catalyzed reaction because of the synthetic difficulty of such reagent due to the high reactivity of azulenes to organolithium and magnesium reagents to produce dihydroazulene derivatives.[5] From the viewpoint of general usage of the transition metal-catalyzed reaction in the chemistry of azulenes, we focused on the development of a versatile organometallic reagent of azulenes. The Stille cross-coupling of organotin compounds with a variety of organic electrophiles, catalyzed by palladium, provides an efficient method for carbon–carbon bond formation.[1,6] Functionalization of azulene in a seven-membered ring is rather difficult so far, although 1,3-positions of the system can be easily functionalized by the electrophilic substitution. Therefore, we examined the stannylation of azulenes in a seven-membered ring and the potential of the reagents for the Stille cross-coupling reaction. Herein we report the preparation of the first versatile organometallic reagents of azulenes, 6-(tri-*n*-butylstannyl)azulenes (**1a** and **1b**) and the successful application to Pd(0)-catalyzed Stille cross-coupling reaction of **1a** and **1b** with aryl and azulenyl halides to demonstrate the utility of the reagents for the carbon–carbon bond formation.

The first 6-stannylazulenes (**1a** and **1b**) were synthesized from 6-bromoazulenes (**2a** and **2b**) via Pd(0)-catalyzed direct stannylation with bis(tri-*n*-butyltin) (**3**).[7] The coupling reaction of diethyl 6-bromoazulene-1,3-dicarboxylate (**2a**)[8] with **3** in the presence of a catalytic amount of $Pd(PPh_3)_4$ in refluxing toluene for 1 day provided the desired diethyl 6-(tri-*n*-butylstannyl)azulene-1,3-dicarboxylate (**1a**) in 69% yield. Likewise, 6-(tri-*n*-butylstannyl)azulene (**1b**) was prepared from 6-bromoazulene (**2b**)[8] with **3** in 49% yield (Scheme 1). These organotin compounds are stable and are easily characterized by usual spectroscopic analysis.[9]

To demonstrate the transformations using the 6-stannylazulenes (**1a** and **1b**), we conducted the Stille cross-coupling reaction with aryl and azulenyl halides to produce 6-aryl- and biazulenes. The results of the reac-



2a: R = COOEt
2b: R = H

1a: R = COOEt
1b: R = H

Scheme 1.

Keywords: azulenyl-tin compound; palladium-catalyzed reaction; Stille reaction; cross-coupling reaction.

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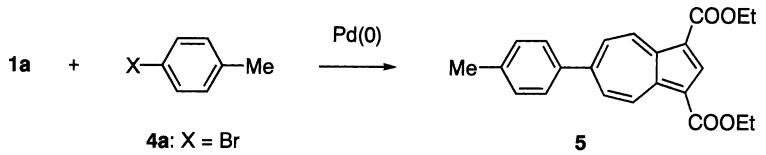
0040-4039/02/$ - see front matter
PII: S0040-4039(01)02347-4

Table 1. Stille cross-coupling reaction of **1a** with **4a** and **4b**[a]



4a: X = Br
4b: X = I

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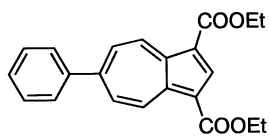
Entry	X	Catalyst	Ligand	Additive	Solvent	Yield (%)[b]				
						5	**6**	**7a**	**8a**	**1a**
1	Br	$Pd(PPh_3)_4$			Toluene	16	52	12	5	0
2	I	$Pd(PPh_3)_4$			Toluene	8	30	25	2	11
3	Br	$Pd_2(dba)_3$	$PtBu_3$		Dioxane	45	–	14	11	0
4	Br	$Pd_2(dba)_3$	$PtBu_3$	CsF	Dioxane	74	–	8	5	0
5	I	$Pd_2(dba)_3$	$PtBu_3$		Dioxane	11	–	4	6	61
6	I	$Pd_2(dba)_3$	$PtBu_3$	CsF	Dioxane	61	–	4	6	22
7	Br	$Pd_2(dba)_3$	BINAP[c]		Dioxane	13	17	26	2	0
8	Br	$Pd_2(dba)_3$	BINAP[c]	CsF	Dioxane	35	17	5	2	0

[a] Reactions of **1a** (0.2 mmol) with **4a** or **4b** (0.6 mmol) were carried out at reflux temperature for 24 h by using 10 mol% Pd(0) catalyst, ligand (Pd/P = 1:2), and 2.2 equiv. of CsF in 20 ml of the solvent.
[b] All yields are isolated yields.
[c] BINAP: 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl.

tion of **1a** with 4-bromo- and 4-iodotoluenes (**4a** and **4b**) are summarized in Table 1. In our initial experiments, **1a** proved to be inefficient in the cross-coupling reaction under typical conditions for the reaction with aryl halides.[10] The reaction of **1a** with **4a** in the presence of $Pd(PPh_3)_4$ catalyst produced the desired diethyl 6-(4-tolyl)azulene-1,3-dicarboxylate (**5**) in 16% yield together with a significant amount of undesired diethyl (6-phenyl- and azulene)-1,3-dicarboxylate (**6**[11] and **7a**[12]) and tetraethyl 6,6′-biazulene-1,1′,3,3′-tetracarboxylate (**8a**) (entry 1) (Chart 1). Using **4b** instead of **4a** increased the recovery of **1a** (entry 2). As seen from Table 1, the choice of the catalytic system was very important for the success of the reaction of **1a**. Substitution of the $Pd(PPh_3)_4$ catalyst with $Pd_2(dba)_3/PtBu_3$ in the catalytic protocol resulted in a significant increase of the desired cross-coupling product **5a** (entry 3). A fluoride-activation strategy,[13] which was utilized for the activation of the organotin compound, was effective for this Stille cross-coupling reaction. The addition of CsF in the catalytic protocol increased the desired coupling product **5** up to 74% yield (entry 4). While good conversions were obtained by using **4a**, the use of **4b** was unfavorable under the reaction conditions, which decreased the conversion ratio of the catalytic reaction significantly (entries 5 and 6). The use of BINAP as a ligand did not afford satisfactory results either in the presence or absence of CsF (entries 7 and 8).

To test the generality, the cross-coupling reaction with several aryl bromides was conducted under the reaction conditions. The results of the cross-coupling reaction of **1a** and **1b** with aryl bromides are summarized in Table 2. The electron-deficient aryl bromide, 4-bromonitrobenzene was efficiently reacted with **1a** to afford the coupled product **9a** in high yield (entry 1). Under similar conditions, the reaction of **1a** with 4-bromoacetophenone also afforded the desired coupling product **9b** in good yield (entry 2). In the case of the reaction of **1a** with electron-rich bromide, 4-bromoanisole, the reaction also proceeded smoothly under our reaction conditions to give the cross-coupling product **9c** (entry 3).

The fluoride-activation strategy was also effective for the catalytic protocol of **1b** with **4a**. The reaction of **1b** with **4a** afforded the desired cross-coupling product **9d**[3,14] under similar Pd(0)-catalyzed conditions (entries 4 and 5). On the whole, **1b** also reacted rapidly with a variety of aryl bromides including an electron-rich one under Pd(0)-catalyzed conditions, and generally the isolated yields of the cross-coupling product were above 60% (entries 6–8).



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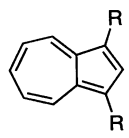
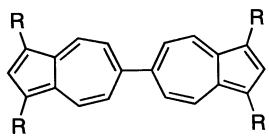


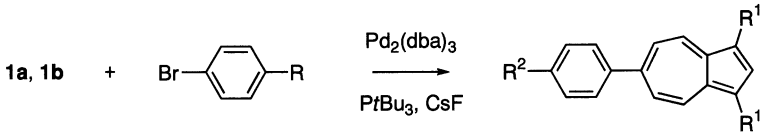
7a: R = COOEt
7b: R = H



8a: R = COOEt
8b: R = H

Chart 1.

Table 2. Stille cross-coupling reaction of **1a** and **1b** with aryl bromides[a]



9a: R^1 = COOEt, R^2 = NO_2 **9d**: R^1 = H, R^2 = Me
9b: R^1 = COOEt, R^2 = COMe **9e**: R^1 = H, R^2 = NO_2
9c: R^1 = COOEt, R^2 = OMe **9f**: R^1 = H, R^2 = COMe
9g: R^1 = H, R^2 = OMe

Entry	Reagent	R	Time (h)	Products (yield/%)[b]		
1	**1a**	NO_2	2	**9a** (85)	**7a** (5)	**8a** (10)
2	**1a**	COMe	2	**9b** (65)	**7a** (4)	**8a** (5)
3	**1a**	OMe	2	**9c** (65)	**7a** (5)	**8a** (3)
4	**1b**	Me	24	**9d** (58)	**7b** (10)	**8b** (31)
5[c]	**1b**	Me	24	**9d** (27)	**7b** (18)	**8b** (32)
6	**1b**	NO_2	2	**9e** (83)	**7b** (5)	**1b** (5)
7	**1b**	COMe	4	**9f** (67)	**7b** (0)	**1b** (1)
8	**1b**	OMe	6	**9g** (63)	**7b** (6)	**1b** (8)

[a] Reaction conditions: **1a** (0.2 mmol) or **1b** (0.3 mmol), aryl bromides (0.6 and 0.9 mmol, respectively), $Pd_2(dba)_3$ (10 mol%), P*t*Bu_3 (40 mol%), CsF (2.2 equiv.), dioxane (20 and 30 ml, respectively), refluxed under an Ar atmosphere.
[b] All yields are isolated yields.
[c] The reaction was carried out without an addition of CsF.

To demonstrate the scope of this procedure, attempts were made for the preparation of 6,6′- and 2,6′-biazulenes using the cross-coupling reaction of **1a** with 6- and 2-azulenyl bromides. Preparation of biazulenes has been achieved by homo-coupling reaction of azulenyl halides[15] or stepwise reaction to prepare the two azulene rings.[16] However, selective synthesis of unsymmetrical biazulenes is significantly difficult so far because of the restriction of the synthetic methods. We then applied our new 6-stannylazulene **1a** to the selective synthesis of biazulenes including unsymmetrical ones. Under the analogous conditions of the reaction with aryl bromides, **1a** reacted smoothly with 6-bromoazulenes (**2a** and **2b**) to afford 6,6′-biazulenes (**8a** and **10**) in 68 and 45% yields, respectively. Similarly, the present method could be applied to the selective synthesis of 2,6′-biazulene **11**.[15b] The reaction of **1a** with 2-bromoazulene under the Pd(0)-catalyzed conditions afforded **11** in 51% yield (Chart 2).

As stated above, the first organotin reagents of azulenes, 6-stannylazulenes (**1a** and **1b**), were prepared by the Pd(0)-catalyzed direct stannylation of 6-bromoazulenes (**2a** and **2b**), and their application in Pd(0)-catalyzed Stille cross-coupling reaction with aryl and azulenyl halides was investigated. In fact, our new stannylazulenes were effective in the Stille cross-coupling reaction to afford 6-aryl- and biazulenes. This initial study shows the potential utility of the new transition metal-catalyzed reaction for the difficult functionalization of azulenes in a seven-membered ring. Investigation into the scope and application of the methodology is currently under way in our laboratories.

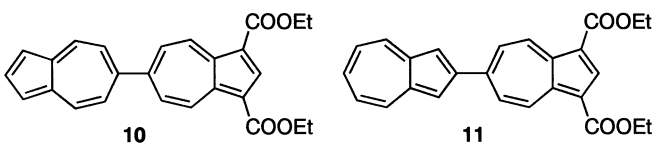


Chart 2.

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9. Selected spectral data for **1a** and **1b**. **1a**: red oil; IR (neat): ν_{max} 1694 (C=O) cm^{-1}; UV–vis (CH_2Cl_2): λ_{max} (log ε) 235 (4.52), 275 (4.44), 311 (4.65), 377 (4.06), 502 (2.88) nm; ^1H NMR ($CDCl_3$): δ 9.63 (d, $J=10.0$ Hz, 2H), 8.83 (s, 1H), 7.96 (d, $J=10.0$ Hz, 2H), 4.44 (q, $J=7.1$ Hz, 4H), 1.58 (m, 6H), 1.46 (t, $J=7.1$ Hz, 6H), 1.35 (tq, $J=7.3$, 7.3 Hz, 6H), 1.21 (m, $J=7.8$ Hz, 6H), 0.90 (t, $J=7.3$ Hz, 9H). **1b**: blue oil; UV–vis (CH_2Cl_2): λ_{max} (log ε) 238 (4.16), 286 (4.74), 332 (3.70), 339 (3.67), 347 (3.83), 575 (2.51), 620 (2.44), 682 (2.01) nm; ^1H NMR ($CDCl_3$): δ 8.22 (d, $J=9.3$ Hz, 2H), 7.88 (t, $J=3.8$ Hz, 1H), 7.36 (d, $J=3.8$ Hz, 2H), 7.35 (d, $J=9.3$ Hz, 2H), 1.57 (m, 6H), 1.35 (tq, $J=7.3$, 7.3 Hz, 6H), 1.14 (m, 6H), 0.89 (t, $J=7.3$ Hz, 9H).
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